

Efforts Towards the Cross Coupling of Acylsilanes and Electrophiles via a Metal-Catalyzed Brook Rearrangement

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Boston College
The Graduate School of Arts and Sciences
Department of Chemistry

EFFORTS TOWARDS THE CROSS COUPLING OF ACYLSILANES AND
ELECTROPHILES VIA A METAL-CATALYZED BROOK REARRANGEMENT

A dissertation
by
CAROLYN A. HEUSSER

Submitted in partial fulfillment of the requirements for the degree of
Master of Science

December 2013

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2013

“Success is not final, failure is not fatal: it is the courage to continue that counts.”

-Winston Churchill

EFFORTS TOWARDS THE CROSS COUPLING OF ACYLSILANES AND ELECTROPHILES VIA A METAL-CATALYZED BROOK REARRANGEMENT

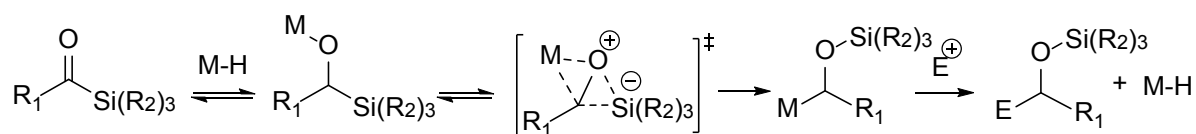
Carolyn A. Heusser

Thesis Advisor: Jeffery A. Byers

Abstract

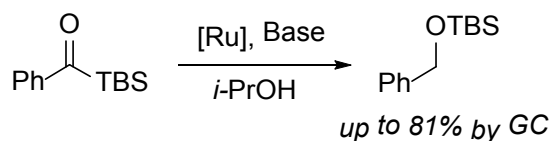
Chapter 1: There are a limited number of examples of metal-catalyzed Brook rearrangements in the literature, none of which involve ruthenium, rhodium, or iridium which are common ketone hydrogenation catalysts. The content of this chapter introduces the traditional Brook rearrangement and its advantages and disadvantages in chemical synthesis. Furthermore, the few examples of metal-catalyzed Brook rearrangements of acylsilanes and structurally similar moieties are discussed.

Metal-Catalyzed Brook Rearrangement



Chapter 2: Utilizing a Brook rearrangement under hydrogenation or transfer hydrogenation conditions opens up a new area of catalytic reactivity that has not been fully explored. To our knowledge, metal complexes based on ruthenium and rhodium have never been shown to catalyze a Brook rearrangement of acylsilanes. This chapter describes the mechanistic implications of a Brook rearrangement under hydrogenation or transfer hydrogenation conditions as well as the first example of a ruthenium-catalyzed Brook rearrangement of aryl acylsilanes.

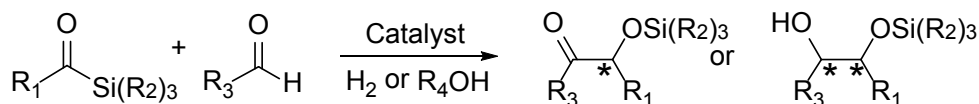
Ruthenium-Catalyzed Brook Rearrangement of Aryl Acylsilanes



Chapter 3: Pioneering work performed by Jeffrey Johnson and co-workers in the area of catalytic coupling of acylsilanes and various electrophiles showed that formation of new C-C bonds through a Brook rearrangement can be a powerful synthetic tool. In this chapter, we investigate an intermolecular coupling of aryl acylsilanes and aldehydes through a metal-catalyzed Brook rearrangement under transfer hydrogenation conditions to yield two synthetically useful motifs, specifically oxygenated bicyclic compounds. A

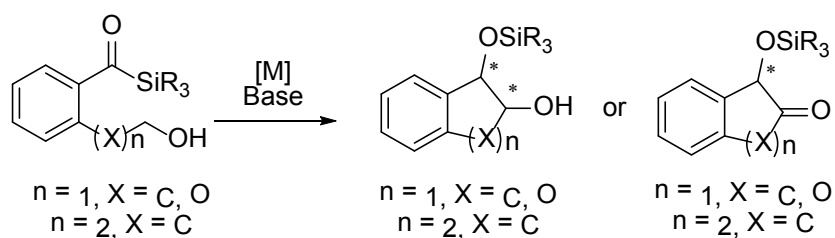
reaction screen was performed on the coupling capabilities of these two species with various ruthenium and rhodium catalysts. The result of the screen was synthesis of a silyl ether acetal through employing the starting material as the reducing equivalent. Additionally, mechanistic insight was gained to further develop the proposed methodology.

Proposed Metal-Catalyzed Intermolecular Coupling of Acylsilanes and Aldehydes



Chapter 4: An intramolecular approach to achieving coupling of acylsilanes and many different types of electrophiles was envisioned as a way of furnishing synthetically useful bicyclic compounds in one step. The focus of this chapter is the synthesis of a novel acylsilane that we proposed could undergo an intramolecular cross coupling reaction under transfer hydrogenation conditions. The conclusion of this chapter outlines the future direction of the project, which entails a new route to an intermolecular cross coupling of acylsilanes and various electrophiles. Published work from Michael Krische's laboratory helped us envision a different type of acylsilane, specifically an α,β -unsaturated acylsilane, in which binding to a metal center would proceed through a π -allyl intermediate. Ongoing efforts in the coupling of α,β -unsaturated acylsilanes with electrophiles are currently underway.

Proposed Metal-Catalyzed Intramolecular Coupling of Acylsilanes and in-situ generated Aldehydes



Acknowledgements

The hardest moments of life are often the greatest learning experiences. These moments give insight into one's character and dreams by pushing one to the brink of what is believed to be possible. Graduate school has been the most emotionally, physically and intellectually challenging experience of my life, yet I'm certain the gain has outweighed the loss.

"What is the point of my hard work?" I believe every graduate student asks him/herself this fundamental question at some point. Each must come to a sound conclusion as to why researching something that may not necessarily be revolutionizing is worth devoting your whole life to. Personally, my work has always been for the greater good; something outside of myself and much stronger than myself. "Whatever you do, do it all for the glory of God" (1 Cor. 10:31). It has become exceptionally apparent to me that chemistry is fickle; it does not care how much you know or how hard you work; good results are often independent of one's effort. Thus, being able to put my worth in the Truth that does not change has been the motivation to tackle the challenges I have faced. Graduate school has exposed strengths and weaknesses in me, but thankfully God's power is made perfect in weakness.

The support of those around me—family, friends and advisers has been imperative in my journey. Without the love and encouragement I have received from those closest to me, I never would have been successful in completing my goals. I would first like to thank my parents, for their godly advice, love, and attentiveness. Without their example of compassion, I would not know how to care for those around me. Leading by example is not always an easy endeavor, but they have always demonstrated honesty, patience, and unconditional love towards my siblings and I. I am forever grateful to God for blessing me with such great role models.

One of the aspects that drew me to Boston College for my graduate studies was the sense of community. The atmosphere of learning and supporting fellow researchers makes Boston College a very unique place. My classmates have been extremely cohesive and concerned with one another's well-being from the very beginning and I'm honored to be a part of such a prestigious and unified graduate program. I am thankful for my advisor, Jeffery Byers, who has put much effort and time into my education. Without his acceptance of me into his laboratory, my experience would have been much different. I'd also like to thank Amir Hoveyda and Marc Snapper for serving on my thesis committee. Professor Snapper has given gentle guidance and unwavering encouragement to me in the pursuit of my academic accomplishments. It is a rare, yet wonderful occurrence when you can go to someone with any problem and know they will have your best interest in mind.

Without a doubt, the students of Boston College have had the greatest impact on me. Each member of the Byers laboratory holds a very special place in my heart. I'd like

to thank Hilan Kaplan, Jessica Drake, Ashley Biernesser, Cesar Manna, Ben Reiner, Mikey Wojnar and Lauren Yablon for assisting me with chemistry, putting up with me on my bad days, dancing with me on my good days, and caring about me as an individual. Hilan has been the most attentive and helpful mentor during my graduate career and without his wealth of knowledge and never-ending willingness to give time for others, I would not have learned as much as I have. Lastly, I'd like to thank Lisa Stankee for being my closest friend, confidant, and sister-in-Christ during this period of my life. Her encouragement and loving example has helped me remember what my ultimate goal and purpose in graduate school has been.

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List of Abbreviations

Å	angstrom
Ac	acetyl
AD	asymmetric dihydroxylation (AD-mix) (containing potassium osmate, potassium ferricyanide, potassium carbonate and phthalazine adduct with dihydroquinine (α) or phthalazine adduct with dihydroquinidine (β))
Ar	aryl (substituted aromatic ring)
ARC	anion relay chemistry
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bm	broad medium (IR)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bs	broad strong (IR)
Bu	butyl
bw	broad weak (IR)
cat	catalyst
COD	cyclooctadiene
Conv.	conversion
Cy	cyclohexyl
d	day(s); doublet (NMR)
δ	chemical shift (in ppm)

DBU	1,8-diazabicycloundec-7-ene
DCE	dichloroethane
dpce	1,2-bis(dicyclohexylphosphino)ethane
DENEB™	oxo-tethered Ru(II) complex owned by Takasago International Corporation
DIBAL-H	diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
E [⊕]	electrophile
<i>ee</i>	enantiomeric excess
equiv	equivalent(s)
ESI+	electrospray ionization (positive ion mode)
Et	ethyl
g	grams(s)
GC	gas chromatography
GCFID	gas chromatography flame ionization detector
h	hour(s)
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry

h ν	visible light
Hz	hertz
IBX	2-iodoxybenzoic acid
<i>i</i> -Pr	isopropyl
IR	infrared spectroscopy
<i>J</i>	coupling constant in Hz (NMR)
L	liter(s); ligand
M	molarity (mol / L); mega (MHz)
<i>m</i>	<i>meta</i>
m	milli; multiplet (NMR); medium (IR)
μ	micro
Me	methyl
min	minute(s)
mol	mole(s)
MS	mass spectrometry
<i>n</i>	normal (unbranched alkyl chain)
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
p	pentet (NMR)
pent	pentyl
Ph	phenyl

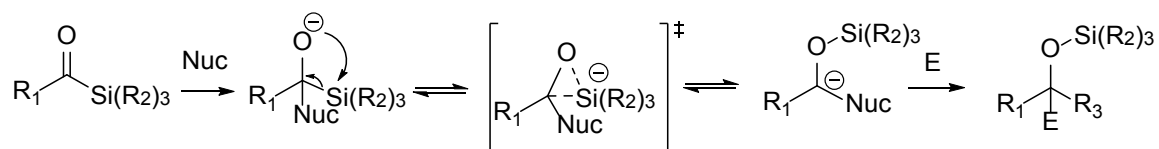
pica	α -picolylamine
ppm	parts per million
Pr	propyl
q	quartet (NMR)
R _L	large R group
R _M	medium R group
R _S	small R group
rt	room temperature
s	singlet (NMR); strong (IR); second(s)
sept	septet (NMR)
<i>t</i>	tertiary alkyl chain
t	triplet (NMR)
TADDOL	$\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TES	triethylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
td	triplet of doublets (NMR)
temp	temperature
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	<i>para</i> -toluenesulfonyl
tt	triplet of triplets (NMR)

UV	ultraviolet
v/v	volume / volume
w	weak (IR)
w/w	weight / weight
X	any halogen

CHAPTER 1
HISTORY OF THE BROOK REARRANGEMENT

1.1 Introduction

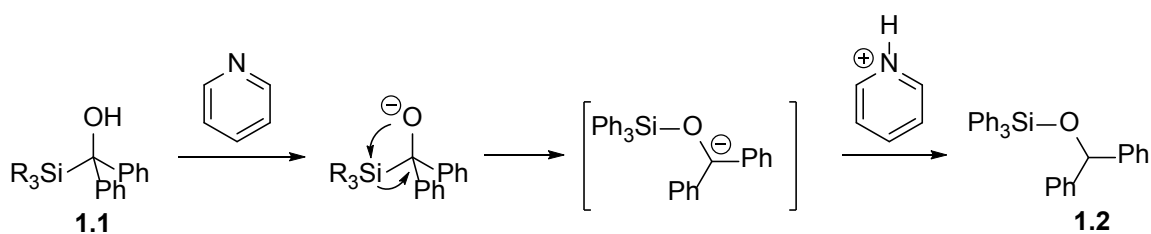
Efficient access and facile derivatization of small complex molecules continues to be an important facet of synthetic organic chemistry. The Brook rearrangement, discovered and studied by Adrian Brook in the late 1950's to the 70's, is an exceptional method for atom-economic transformations.¹ Initiated by a nucleophile, a Brook rearrangement is a silyl group migration from carbon to oxygen that leads to new carbon-carbon bonds while simultaneously protecting an alcohol and, in some cases, forming a stereogenic center (**Scheme 1.1**). The rearrangement can take place over a range of multiple atoms, with the most recent report of a long-range iteration spanning 8 atoms.² The requirement of two independent chemical moieties, one for activation of the small molecule and one for protection of the functional group, is eliminated by the dual-activity of this transformation. Thus, the Brook rearrangement is a compelling strategy for the rapid assembly of small complex molecules.



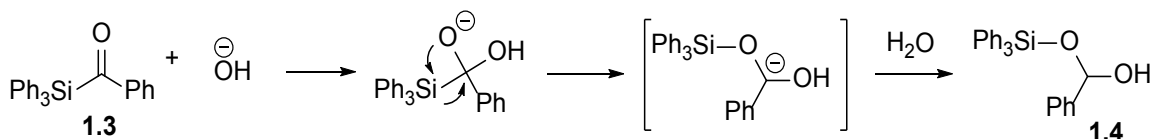
Scheme 1.1: General Mechanism of a 1,2-Brook Rearrangement

Brook's first published work in 1958 outlined the subjection of α -hydroxy silanes to pyridine (**Scheme 1.2**).^{1b} What he discovered was the formation of silyl ether product **1.2** as the result of a silyl migration from carbon to oxygen of α -hydroxy silane **1.1**. The initial trends that were observed in the case of α -hydroxy silane **1.1** indicated that the rearrangement was slower for alkyl substituents over aryl substituents and that the groups

substituting the silicon, whether aryl or alkyl, had little effect on the rearrangement. Along with the help of Norman Schwartz, Brook further elaborated the rearrangement to other substrates, specifically acylsilanes in 1962.³ In work published that year, Brook and Schwartz described a step-wise attack of a hydroxide ion on the carbonyl carbon of acylsilane **1.3**. They proposed the attack lead to formation of an alkoxide which underwent a Brook rearrangement, leading to formation of the observed silyl ether product **1.4** (**Scheme 1.3**). More insight was gained in 1967, when Brook reported that acylsilanes would undergo the Brook rearrangement through a photochemical process upon irradiation.^{1d} With regard to stereochemistry, Brook reported retention of configuration at silicon and inversion of configuration at carbon for tetrahedral substrates. However, it has since been determined that although in most cases there is a defined stereochemical outcome of the Brook rearrangement, there isn't always a trend across substrates.⁴

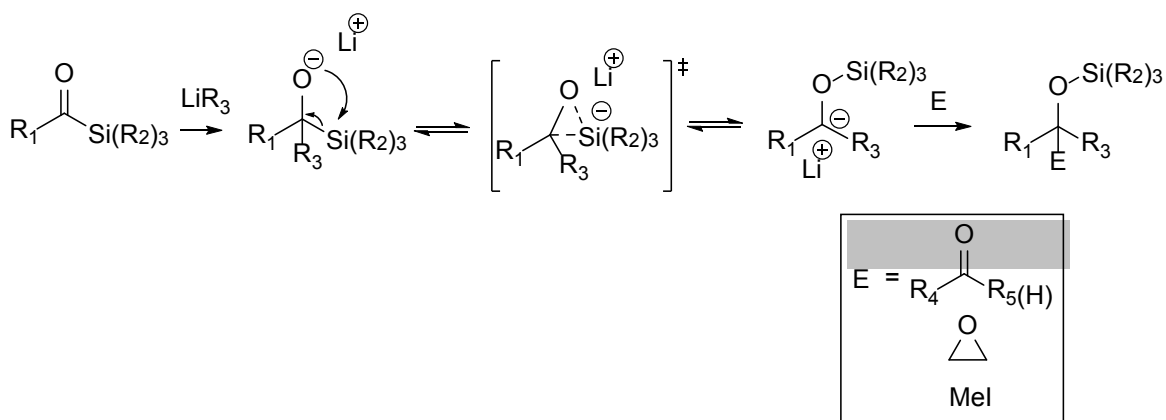


Scheme 1.2: First Reported Brook Rearrangement.



Scheme 1.3: First Reported Brook Rearrangement of Acylsilanes.

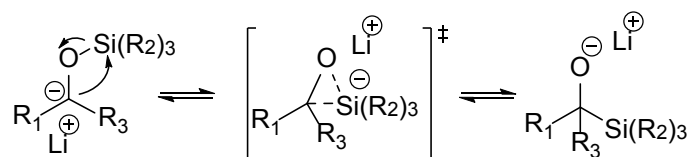
Based on the work demonstrated in previous years, in 1974 Brook concluded that the rearrangement of α -hydroxy silanes could be facilitated by not only base, but also metals and organometallic reagents such as sodium, potassium and organo-lithium species.^{1a} The Brook rearrangement of acylsilanes has since been accomplished largely with the assistance of organo-lithium reagents in the presence of a highly polar solvent (**Scheme 1.4**).⁵ The addition of the lithium species leads to formation of a lithium alkoxide which can reversibly attack silicon and form a new carbanion. Brook and others have proposed that this proceeds through a transition state in which silicon is pentavalent.^{1,4,5} The lithiated carbanion can then attack a carbon electrophile which leads to a new C–C as well as a Si–O bond. We have deemed this type of organo-lithium-promoted Brook rearrangement as the “traditional” route, which will be expanded upon in the following sections.



Scheme 1.4: The traditional Brook rearrangement with organo-lithium reagents.

The Brook rearrangement is reversible and the retro-Brook rearrangement, migration of silicon from oxygen to carbon, has also been thoroughly studied (**Scheme 1.5**).⁶ In the presence of strongly coordinating counterions such as lithium, the retro-

Brook rearrangement is often favored. Retro-Brook rearrangements are also known to span across multiple atoms.



Scheme 1.5: The Retro-Brook Rearrangement.

As alluded to, the equilibrium between the Brook rearrangement/retro-Brook rearrangement is dependent on a number of factors. The formation of a strong silicon-oxygen bond is favored over a silicon-carbon bond by approximately 50 kcal/mol, which is the primary driving force in the forward direction. However, depending on the counterion, the rearrangement is also dictated by the relative ion pair strengths of the alkoxide versus the carbanion. One of the major factors that affects these energies lies within the identity of the solvent employed in the rearrangement. Highly polar solvents are commonly employed to drive the Brook rearrangement in the forward direction by decreasing the counterion interaction with the alkoxide. The role the solvent plays will be discussed further in a later section.

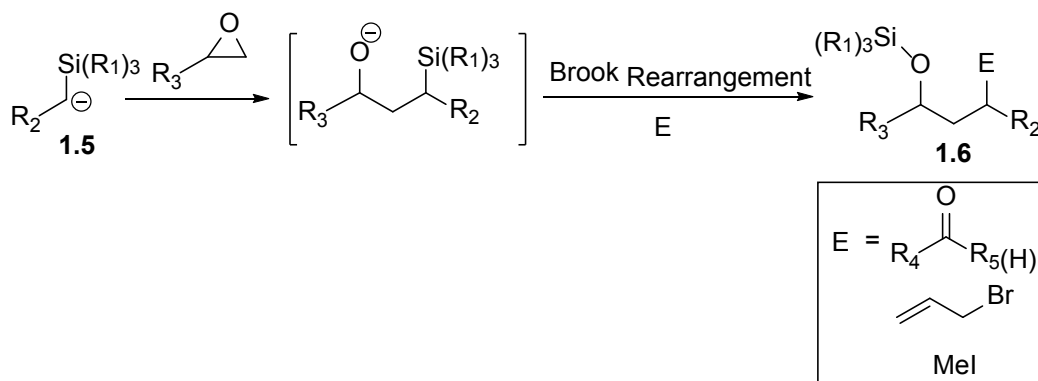
1.2 Applications of the Brook Rearrangement in Chemical Synthesis

The novelty of the Brook rearrangement has briefly been introduced as a simple process with high atom-economy. However, the Brook rearrangement is much more fundamentally useful due to the fact that it leads to the formation of protected alcohols in a single, complexity-building step. One of the most widely used synthetic organic

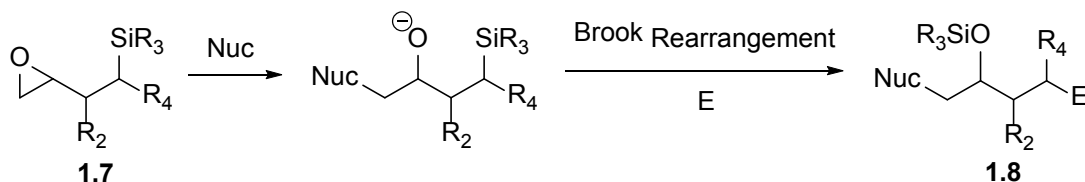
transformations in multi-step syntheses is protection of an alcohol. Accordingly, the importance of this reaction has led to the development of a plethora of groups that can be used to protect specific types of functionalities.⁷ Silicon-containing moieties are often employed as capable protecting groups due to their ease of installation and removal with respect to the protection of alcohols.⁷ The Brook rearrangement is an unusual example of a way to install a protecting group without having to increase the number of steps in a synthetic route. Although this is one unique aspect of the chemistry, there are many other examples of the utility of the Brook rearrangement in chemical synthesis.

One of these examples comes from the laboratory of Amos B. Smith III, who has coined the term “Anion Relay Chemistry (ARC)” to describe how a negative charge flows through a molecule during a chemical reaction.⁸ There are two main categories of ARC, namely “through-bond” or “through-space,” which help describe how the anion is transferred. Furthermore, the “through-space” category can be broken down further into two main divisions, specifically type I and type II. In type I ARC reactions the anion that is transferred back to its original location (atom) at the end of the process (**Scheme 1.6**). In type II reactions, the anion ends up on a different atom at the end of the process (**Scheme 1.7**). Smith has demonstrated examples of ARC through various multi-component reactions, most of which also involve a Brook rearrangement.⁹ One of the most interesting examples was published in 2008, in which he demonstrated that silyl anion **1.5** would react with epoxides and undergo a 1,4-Brook rearrangement to form a new carbanion (**Scheme 1.6**).⁸ The carbanion could be trapped in the presence of an electrophile to yield substituted silyl ether **1.6**. The example below can be categorized as

a type I, through space transformation in which the anion is relayed from carbon to oxygen and then back to the original carbon.



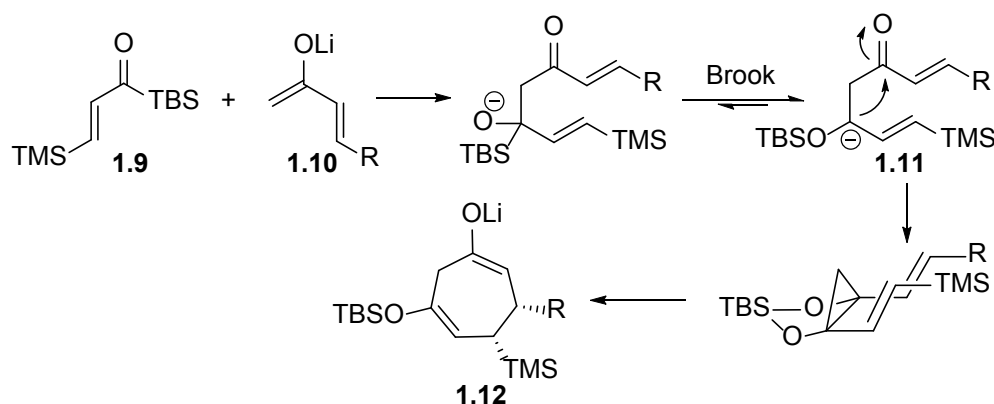
Scheme 1.6: Synthesis of Substituted Silyl Ethers through a 1,4-Brook Rearrangement: An Example of Type I Anion Relay Chemistry.



Scheme 1.7: Synthesis of Substituted Silyl Ethers through a 1,4-Brook Rearrangement: An Example of Type II Anion Relay Chemistry.

Other work utilizing the Brook rearrangement in chemical synthesis involves medium-size ring formation strategies. Reports from Kei Takeda and others in 1995 revealed a [3+4] annulation reaction that utilized a Brook rearrangement (**Scheme 1.8**).¹⁰ Subjection of α,β -unsaturated acylsilane **1.9** to lithium enolate **1.10** resulted in a 1,2-Brook rearrangement, which furnished a new carbanion **1.11**. The carbanion underwent cyclopropanation and then an oxanion-accelerated Cope rearrangement which gave the seven-membered ring **1.12** in high yield and as one major diastereomer. The mechanistic

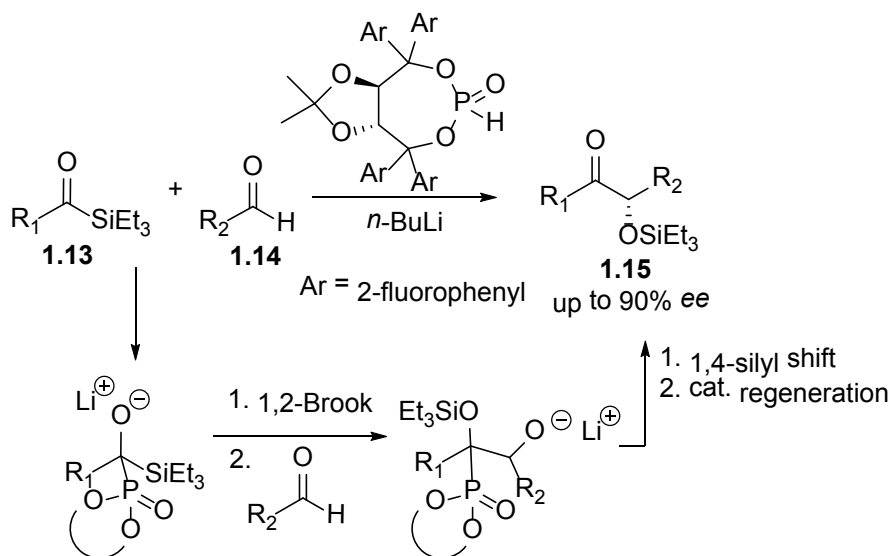
pathway proposed was chosen over a Michael addition due to the observed stereochemical outcome of the reaction.



Scheme 1.8: Synthesis of Medium-Sized Rings through a 1,2-Brook Rearrangement.

Jeffrey Johnson and coworkers at the University of North Carolina Chapel Hill have worked on using the Brook rearrangement in coupling chemistry with the assistance of various catalysts.¹¹ His impact on this area of chemistry will be described in more detail in **Chapter 3**, but as an introduction, his laboratory has demonstrated catalytic coupling of acylsilanes with aldehydes and ketones. One of the most impressive examples is a metallophosphonate-promoted coupling of aryl acylsilanes **1.13** and aryl or heterocyclic aldehyde **1.14** (**Scheme 1.9**).¹¹ Through the use of a chiral ligand, the Johnson laboratory could synthesize the cross-silyl benzoin complex **1.15** in good yields and high enantiomeric excess. The proposed mechanism for this transformation involves a 1,2-Brook rearrangement of the acylsilane and then a 1,4-silyl group transfer.

¹¹ For full list of references see Chapter 3.



Scheme 1.9: Enantioselective Synthesis of Cross-Silyl Benzoin Derivatives through a 1,2-Brook Rearrangement.

From the above examples, it is evident that the Brook rearrangement has been used in many different areas of organic synthesis. Although a handful of examples were discussed herein, there are certainly other examples of the Brook rearrangement's utility.¹² The synthesis of complex small molecules seems to be one of the many applications of this transformation which we believe can be developed further.

1.3 Drawbacks of the Traditional Brook Rearrangement

The use of the traditional Brook rearrangement is a powerful tool because it leads to a protected alcohol in one step, makes a new C–C bond and forms a stereogenic center. However, the traditional route also has several important limitations that we believe can be improved upon. First, the stoichiometric use of a basic organo-lithium species is required for the promotion of the rearrangement, which can racemize stereogenic centers

α to the carbonyl.¹³ The use of these reagents limits the scope of the reaction in terms of what acylsilane substrates can be used. One can imagine that any acylsilanes containing acidic protons would not undergo the Brook rearrangement in the presence of an organo-lithium reagent. Second, the rearrangement is often promoted in highly polar solvents due to the need for decreased interaction between the alkoxide and counterion (in this case lithium). One such solvent that is often employed is HMPA, which is known to cause cancer in animal models.¹⁴ Addition of HMPA forms a more reactive alkoxide through the ligation of lithium counterions, which can then attack silicon to undergo the Brook rearrangement.⁸ Third, the trapping of a lithiated carbanion is only achieved by conventional electrophiles, such as carbonyl-containing compounds, further limiting the application of this chemistry. Lastly, it is also exceptionally difficult to control the stereochemistry of the electrophilic trapping without the use of a chiral auxiliary, which calls for longer synthetic routes to the acylsilane substrate. This further supports the novelty of the Johnson chemistry in that the stereochemistry is controlled by the catalyst.

Significant improvements to the traditional route could be accomplished by the use of a transition metal instead of an organo-lithium reagent. Removing the necessity of strong Brønsted bases and harsh solvents presents a more tolerant, as well as environmentally friendly reaction. Without the requirement for an organo-lithium reagent, the scope of the reaction also increases to a wide variety of acylsilanes. Also, transition metal-alkyl bonds exhibit unique reactivity due to the fact that metals can bond through *d*-orbitals to coordinate many different classes of substrates. The use of a transition metal catalyst could thus widen the scope of available electrophiles to potentially include some non-traditional types, such as olefins. Finally, the

stereochemistry of the transformation could be controlled by judicious choice of metal catalyst. Employing chiral ligands bound to the metal center could direct the Brook rearrangement as well as the incorporation of the electrophile to generate products in a stereocontrolled fashion.

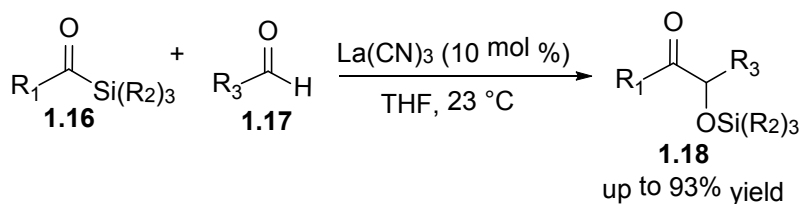
1.4 Metal-Catalyzed Brook Rearrangement

To our knowledge, there are a handful of examples of metal-catalyzed Brook rearrangements of acylsilanes presented in the literature.¹⁵ From what we have referenced, only a few detail a transition-metal mediated process.^{15a,b,f} Furthermore, none involve hydrogenation catalysts such as ruthenium, iridium, or rhodium-based complexes. There has been one publication that reported iridium, palladium, platinum, and rhodium as competent catalysts for a Brook rearrangement, but the substrate was not an acylsilane.¹⁶ The discussion included in this section will only focus on the Brook rearrangement of acylsilanes. As mentioned previously, the most relevant work has been performed by Jeffrey Johnson's laboratory, but there are other laboratories who have demonstrated this unique transformation under metal-catalyzed conditions, which will be discussed in detail.

1.4.1. Aluminum and Lanthanum

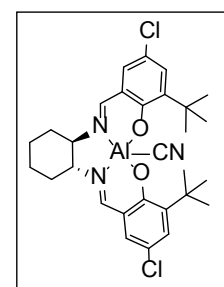
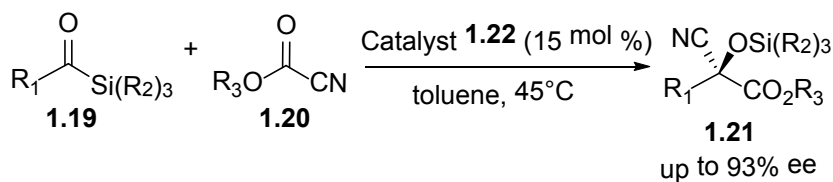
Although the Johnson group has demonstrated metal-catalyzed Brook rearrangements and the reactions they have achieved are very similar to the type of process we set out to accomplish, none have been catalyzed by transition metals. Most of the work published by the Johnson laboratory in the early 2000's focused on the

lanthanum and yttrium cyanide-catalyzed Brook rearrangement of acylsilane **1.16** in order to achieve coupling with various aldehydes, which was an efficient way to undergo a cross-silyl benzoin reaction (**Scheme 1.10**).¹⁷ The reaction was found to be optimal with aryl acylsilanes and aldehydes, but could tolerate alkyl derivatives as well as aryl, alkyl, alkenyl, and alkynyl ketones.^{17b}



Scheme 1.10: Coupling of Acylsilanes and Aldehydes with Lanthanum Catalysts.

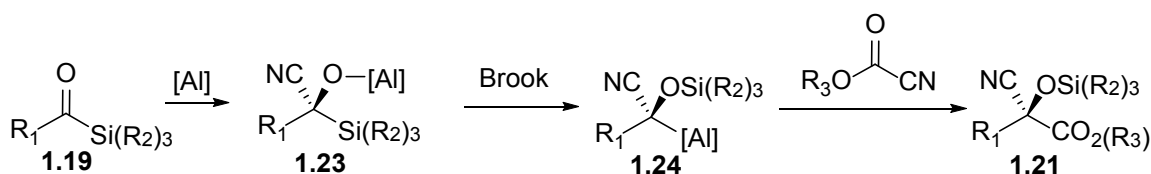
The chemistry demonstrated by the Johnson group has been further elaborated to include reactions of acylsilanes with cyano-esters by employing aluminum catalysts. Also in 2004, the group demonstrated that aluminum salen complex **1.22** could induce enantioselective cyanation and C-acylation of acylsilane **1.19** in an efficient manner (**Scheme 1.11**).¹⁸ The published work portrayed a resourceful route to substituted silyl ether **1.21** in good yields and high enantioselectivities.



Catalyst **1.22**

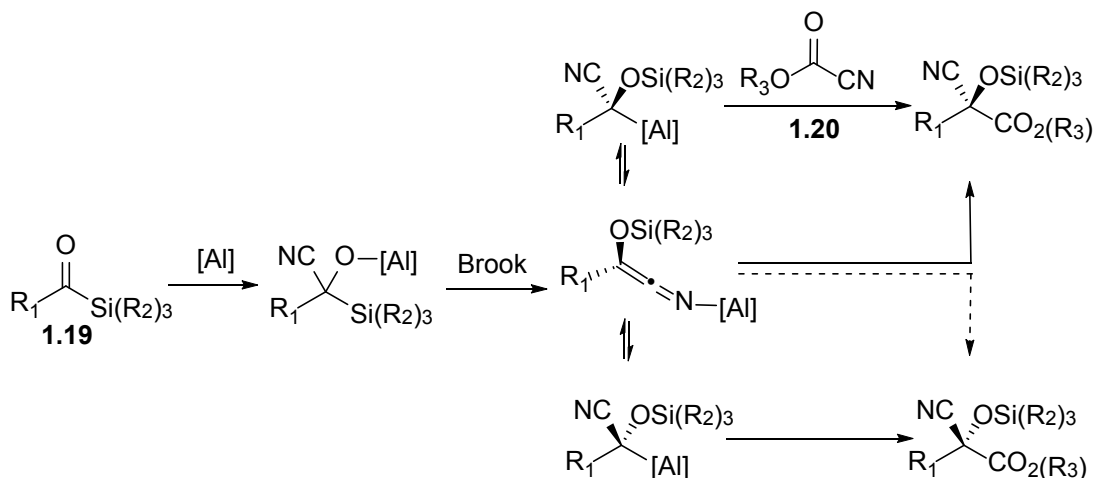
Scheme 1.11: Coupling of Acylsilanes and Cyano Esters with Aluminum Catalysts.

The mechanism for the above reaction was proposed to occur through one of two different pathways. In the first mechanism, the addition of the aluminum-cyano complex **1.22** leads to enantioselective cyanation, forming a new aluminum-alkoxide **1.23** (**Scheme 1.12**). This then undergoes a stereospecific Brook rearrangement to furnish a new aluminum-alkyl **1.24**, which upon addition of the cyano-ester leads to stereospecific acylation to furnish the silyl ether product **1.21**.



Scheme 1.12: Proposed Mechanism for the Aluminum-Catalyzed Brook Rearrangement of Aryl Acylsilanes.

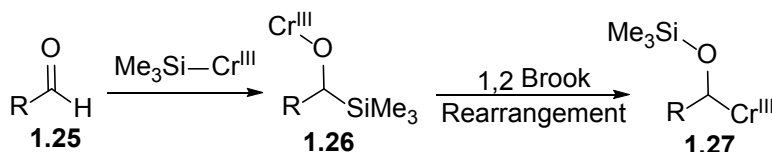
On the other hand, the addition of the aluminum-cyano complex **1.22** could occur in a non-selective fashion, which after Brook rearrangement would result in diastereomeric allenes. (**Scheme 1.13**). These intermediates could then have different rates of acylation, effectively resulting in a kinetic resolution upon addition of cyano-ester **1.20**. It should be noted that no intermediates of the proposed mechanisms were observed, and thus could not be proven.



Scheme 1.13: Proposed Mechanism for the Aluminum-Catalyzed Brook Rearrangement of Aryl Acylsilanes.

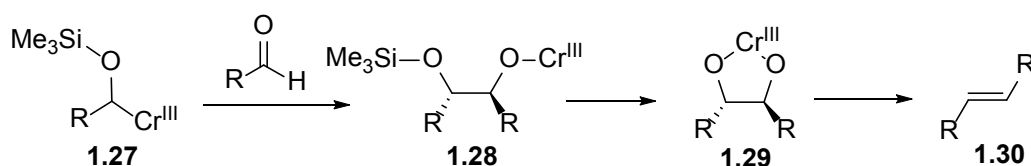
1.4.2. Chromium

Chromium has also been used as a transition metal catalyst for the Brook rearrangement. In 2006, the Falck laboratory demonstrated that aryl and conjugated aldehydes could be converted to chromium alkoxides upon addition of silyl chlorides (**Scheme 1.14**).^{15a} Although the starting material used by the Falck group is not an acylsilane, silyl-metalation of aldehyde **1.25** led to intermediate **1.26** that is essentially a masked acylsilane. Alkoxide **1.26** then underwent a 1,2-Brook rearrangement mediated by the chromium metal center to yield metal-alkyl **1.27**.



Scheme 1.14: Chromium-Catalyzed Brook Rearrangement of Silyl Alkoxides.

Further functionalization of the chromium-alkyl was accomplished by addition of a second equivalent of the aldehyde (**Scheme 1.15**). The authors proposed that migratory insertion of the aldehyde into chromium-alkyl **1.27** led to a new chromium-alkoxide, **1.28** which then underwent loss of the silicon group to form chromium chelate **1.29** with both oxygen atoms. This intermediate was conformationally locked and was found to selectively give the *trans* disubstituted olefin **1.30**. However, a pinacol rearrangement was not ruled out as another possible mechanism. Various olefin products were obtained in yields of up to 95%.



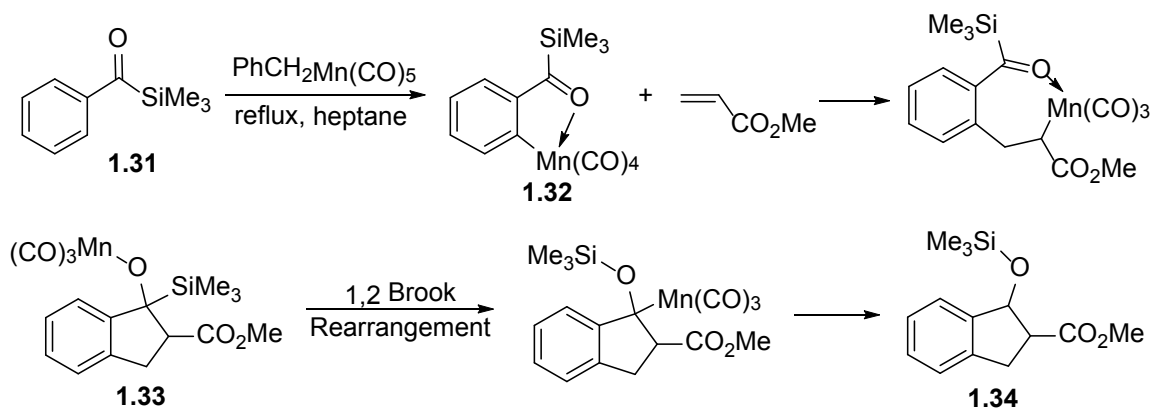
Scheme 1.15: Formation of *trans* Olefins via a Chromium-Catalyzed Brook Rearrangement.

1.4.3. Manganese

An extensive mechanistic study was published in 1994 regarding the reactions of tetracarbonylmanganese complexes of acylsilanes.^{15b} The laboratory of Paul Woodgate undertook investigation of the mechanistic pathways to products they observed from various reaction conditions involving benzoyltrimethylsilane **1.31** and benzylpentacarbonyl-manganese. Upon subjection of acylsilane **1.31** to the manganese complex in refluxing heptane, they report formation of an η^2 -manganese complex **1.32** (**Scheme 1.16**). Addition of methyl propenoate allowed for migratory insertion into the manganese-alkyl bond followed by insertion into the carbonyl of the acylsilane to give the cyclized intermediate **1.33**. The new manganese-alkoxide then underwent a 1,2-

Brook rearrangement followed by reductive cleavage to give the silyl ether derivative

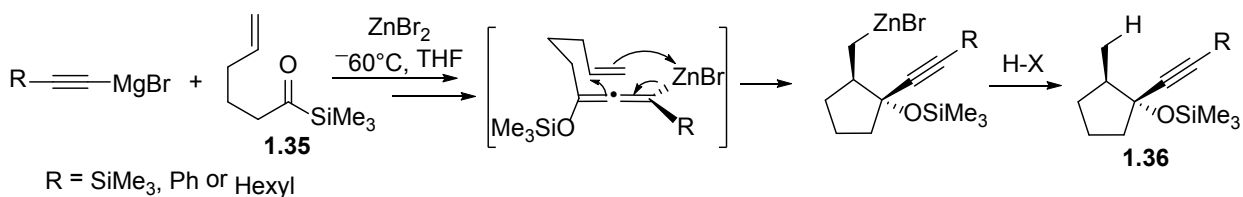
1.34. The silyl ether was one of 4 major products observed from the reaction conditions.



Scheme 1.16: Manganese-Mediated Brook Rearrangement of Silylated Bicycles.

1.4.4. Zinc

In 2005, Ilan Marek and co-workers published an example of a zinc-mediated Brook rearrangement of acylsilanes (**Scheme 1.17**).^{15f} They demonstrated a tandem reaction involving the carbocyclization of propargylic zinc compounds that involved a stereospecific Zn-ene-allene carbocyclization. The reaction lead to the formation of a single diastereomers of the silyl ether substituted ring **1.36**.

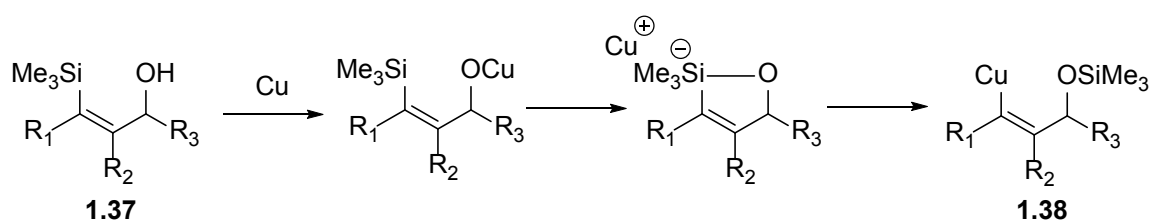


Scheme 1.17: Manganese-Catalyzed Brook Rearrangement of Silylated Bicyclic Compounds.

The formation of the zinc-alkoxide from acylsilane **1.35** upon addition of ZnBr_2 was followed by a 1,2- Brook rearrangement. The relative stability between the resulting silyl ether alkyne and allene allowed for the stereoselective Zn-ene-allene carbocyclization in which the resulting silyl ether and zinc substituents were found to be *trans*. Yields of the desired product ranged from 50% up to 89%.

1.4.5. Copper

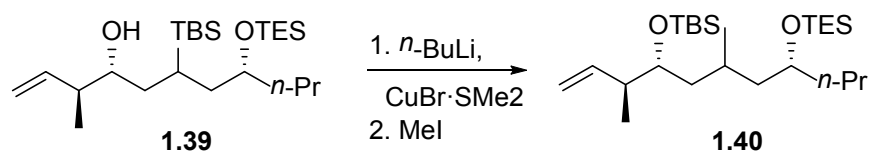
The last examples of a metal-mediated Brook rearrangement involve copper. Takeshi Takeda's laboratory has published work in 2001 and 2002 based on a copper-mediated Brook rearrangement with trimethylsilyl allylic alcohols.¹⁹ Upon subsection of vinylsilane **1.37** to CuI-KF , a proposed transmetalation of silicon to copper occurred which then lead to a Brook rearrangement (**Scheme 1.18**). This allowed for the reaction of silyl ether **1.38** with various electrophiles. Takeda's group has also reported the use of *t*-BuOCu as a Brook rearrangement mediator with the same substrates.



Scheme 1.18: Copper-Mediated Brook Rearrangement of Allylic Silyl Alcohols.

The other example of a copper-mediated Brook rearrangement comes from the laboratory of James Leighton in 2005.²⁰ In their efforts towards the total synthesis of Dolabelide D, treatment of substituted alcohol **1.39** with *n*-BuLi and then $\text{CuBr} \cdot \text{SMe}_2$

and DMPU lead to a 1,4-Brook rearrangement (**Scheme 1.19**). The substrate was then treated with MeI to make a new C–C bond. Their route detailed efficient use of the Brook rearrangement in synthesis as they achieved simultaneous protection of an alcohol and formation of a new C–C bond.



Scheme 1.19: Copper-Mediated Brook Rearrangement of Substituted Alcohols

The limitation of all the metals listed in this chapter is that none are good hydrogenation metals. Ruthenium, rhodium, and iridium are known transition metal catalysts for ketone hydrogenation and we are interested in their ability to catalyze the Brook rearrangement as well.

1.5. References

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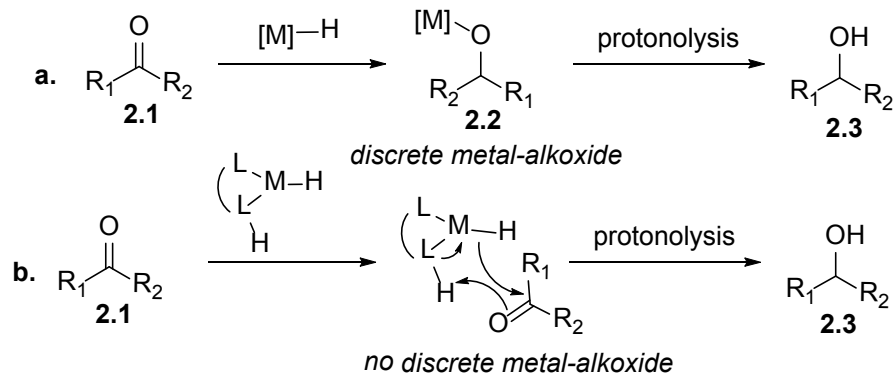
CHAPTER 2

DEVELOPMENT OF A RUTHENIUM-CATALYZED BROOK REARRANGEMENT

2.1 Introduction

Hydrogenation and transfer hydrogenation, the formal addition of dihydrogen across a double bond, are extremely powerful and ubiquitous synthetic tools.²¹ These reactions have been utilized across many disciplines of science and in various industries.²² For example, one of the largest scale hydrogenation reactions is used by the food industry in processing vegetable oils.²³ Although hydrogenation with molecular dihydrogen is traditionally accomplished with heterogeneous catalysts, there are numerous homogeneous transition metal complexes that are capable of catalyzing hydrogenation and transfer hydrogenation reactions of many different substrates.²⁴ Most notably, many of these processes occur in a stereoselective fashion with pro-chiral molecules such as ketones, a method that has proven to be paramount in the synthesis of complex molecules and has led to a 2010 Nobel Prize in chemistry.²⁵

The mechanism of ketone hydrogenation and transfer hydrogenation has been thoroughly studied and is highly dependent on the type of catalyst that is employed.²⁶ Although there are many subdivisions of the mechanism of ketone hydrogenation, the two main categories pertain to inner and outer sphere mechanisms (**Scheme 2.1**).²⁷ In an inner sphere mechanism, binding of ketone **2.1** to the metal leads to formation of a discrete metal alkoxide **2.2**, which upon subsequent protonolysis, affords the desired alcohol **2.3** (**Scheme 2.1a**).



Scheme 2.1: Inner and Outer Scheme Mechanisms of Ketone Hydrogenation.

On the other hand, in an outer sphere mechanism, ketone **2.1** never forms a discrete metal alkoxide, but rather undergoes delivery of the hydride and proton in a concerted process (**Scheme 2.1b**). This usually requires the presence of a cooperative ligand, typically containing nitrogen or oxygen bearing a proton that can be transferred to the substrate. Some of the most famous catalysts built upon this design have been developed by Ryōji Noyori and coworkers, whose contributions were recognized with the 2001 Nobel Prize in Chemistry.²⁸ Heavily based off of calculations that were performed in the gas phase, a concerted mechanism was initially proposed as the energetically preferred pathway with specific ruthenium catalysts.²⁹ Since Noyori's ground-breaking work, however, computational calculations in the liquid phase have been performed by a handful of laboratories, which have shown that a step-wise, solvent-mediated process is the preferred pathway under the reaction conditions.³⁰ The unresolved ambiguity of the mechanism of ketone hydrogenation provided an opportunity for us to gain more understanding by studying the mechanism of acylsilane hydrogenations. Given the

impact and popularity of ketone hydrogenation, experiments to corroborate the computational findings could be of paramount impact.

With regard to ketone substrates, both the inner and outer sphere mechanisms have been well studied. Much less is known about the reduction and hydrogenation of acylsilanes.³¹ Acylsilanes are structurally similar to ketones, but electronically different due to the fact that silicon is α to the carbonyl carbon. We have been interested in the mechanistic aspects of hydrogenation of acylsilanes with respect to a different transformation, the Brook rearrangement, specifically in the area of cross coupling of acylsilanes. At the onset of this project, we had asked ourselves a few probing questions related to the two transformations: would there be a moment in the mechanistic pathway of the hydrogenation of an acylsilane that would allow for a Brook rearrangement to occur, and if so, would this only be allowed with certain classes of catalysts (*i.e.* inner sphere catalysts)? Furthermore, would the rearrangement occur in a stereochemically-controlled fashion if we employed a chiral catalyst? The answers to these questions are addressed in the next section.

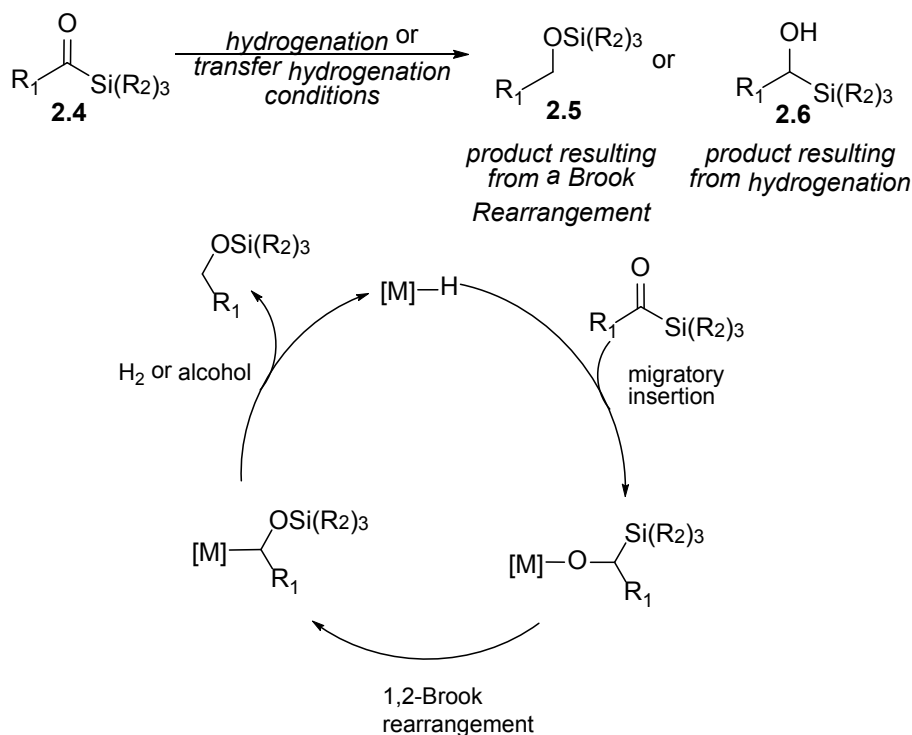
2.2 Application of the Brook Rearrangement in Hydrogenation and Transfer

Hydrogenation Reactions

2.2.1 Experimental Design

Ketone hydrogenation and transfer hydrogenation are both reactions that could be exploited as novel entries to substrates that could undergo a Brook rearrangement, ultimately leading to complex and synthetically valuable products.³² By replacing a ketone with acylsilane **2.4**, subjection to hydrogenation or transfer hydrogenation

conditions could lead to the formation of two possible products, silyl ether **2.5** resulting from a Brook rearrangement, or α -hydroxy silane **2.6** resulting from hydrogenation alone (**Scheme 2.2**). Hydrogenation of acylsilanes followed by the Brook rearrangement would be a useful transformation to gain more mechanistic insight into the process of ketone hydrogenation.



Scheme 2.2: Proposed Reaction Products of Hydrogenation or Transfer Hydrogenation of Acylsilanes.

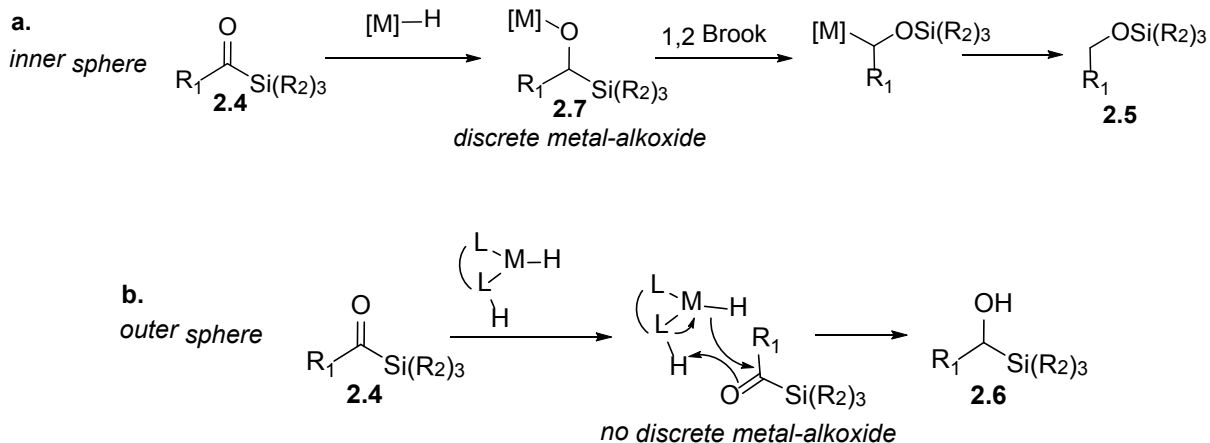
Not only are silyl ethers ubiquitous in synthetic organic chemistry, but we also reasoned that accessing these motifs through a metal-catalyzed hydrogenation or transfer hydrogenation reaction of acylsilanes would shed light on the mechanistic aspects of ketone hydrogenation. In particular, such studies would contribute to further

understanding the involvement of inner versus outer sphere processes in ketone hydrogenation.

2.2.2 Mechanistic Aspects of the Brook Rearrangement

The reaction mechanisms for the hydrogenation and transfer hydrogenation of acylsilanes are presumed to be analogous to those described in section 2.1.1 and can be classified as inner sphere or outer sphere mechanisms (**Scheme 2.3**). When considering an inner sphere process, formation of discrete metal alkoxide **2.7** through addition of acylsilane **2.4** to a metal-hydride could potentially allow for a Brook rearrangement to occur and form the corresponding silyl ether **2.5** (**Scheme 2.3a**). The reaction outcome is dictated by the relative rates of formation of the silyl ether vs. α hydroxyl silane, however the lifetime of metal alkoxide **2.7** must also be considered. If it is short-lived, a Brook rearrangement might not occur and the only observed product would be α -hydroxy silane **2.6**.

However, metal catalysts that are similar in structure to many of Noyori's catalysts (*i.e.* ones that possess a pendant proton donor ligand) would potentially proceed through a different mechanism. Formation of α -hydroxy silane **2.6** where no Brook rearrangement could occur would be the expected product outcome (**Scheme 2.3b**). We speculated as to which types of mechanisms would operate under certain scenarios, but we were pleasantly surprised by our experimental results.



Scheme 2.3: An Inner Sphere Mechanism Versus Outer Sphere Mechanism for the Hydrogenation of Acylsilanes.

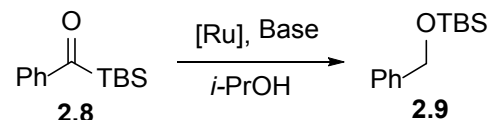
2.3 Discovery of a Ruthenium-Catalyzed Brook Rearrangement under Transfer

Hydrogenation Conditions

2.3.1. Experimental Design

Initial testing of the hydrogenation and transfer hydrogenation of acylsilanes began with designing the experimental procedure and probing a known hydrogenation catalyst. From a logistic standpoint, transfer hydrogenation seemed to be a more experimentally sound option for our initial testing due to the fact that a pressurized hydrogen gas system was not required. Furthermore, although there are many capable transition metals that catalyze the transfer hydrogenation of ketones, we wanted to begin our focus on ruthenium.³³ Ruthenium is an excellent transfer hydrogenation catalyst and many of Noyori's enantioselective complexes are ruthenium(II)-based species.³⁴ We envisioned aryl acylsilane **2.8** to be a suitable substrate to test our hypothesis that

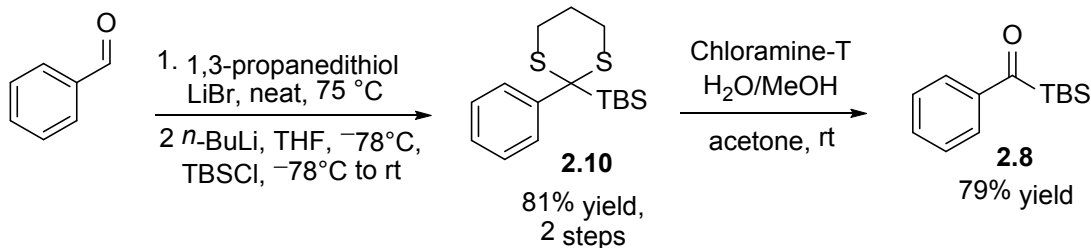
ruthenium could catalyze the Brook rearrangement. We also proposed that subjection of aryl acylsilane **2.8** to a ruthenium-hydride, which could be formed from activation of isopropanol in the presence of base, would result in a Brook rearrangement leading to formation of silyl ether **2.9** (Scheme 2.4).



Scheme 2.4: Proposed Conditions for the Ruthenium-Catalyzed Brook Rearrangement of Acylsilane **2.8**.

2.3.2. Synthesis of Aryl Acylsilane **2.8**

Before testing of the reaction conditions, synthesis of aryl acylsilanes was carried out. Aryl acylsilanes are readily prepared in high yields from commercial available aldehydes in a 3-step synthesis utilizing dithiane intermediates (Scheme 2.5).³⁵ Treatment of benzaldehyde with 1,3-propanedithiol lead to formation of the dithiane-protected aldehyde. Extensive drying of the dithiane-protected aldehyde over P₂O₅ for 24h prior to reaction with *n*-BuLi and trapping with TBSCl was found to be crucial to the yield of the silylated dithiane **2.10**. The silylated dithiane **2.10** could then be converted to acylsilane **2.8** in air, at room temperature upon treatment with chloramine-T, a mild oxidant. Furthermore, substituted aryl groups, as well as various silicon groups can be installed via the dithiane route outlined below in a highly efficient manner.

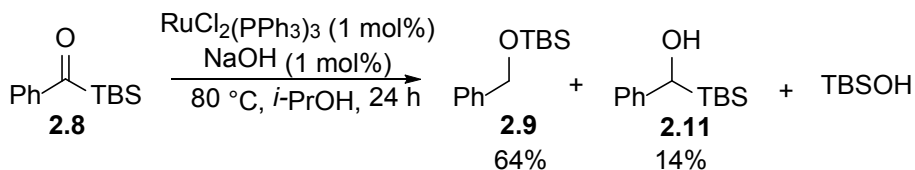


Scheme 2.5: Synthetic Route to Access Acylsilane **2.8**.

The optimized synthetic route allowed for access to multi-gram quantities of aryl acylsilane **2.8**, at which point we began our investigation into a ruthenium-catalyzed Brook rearrangement under transfer hydrogenation conditions.

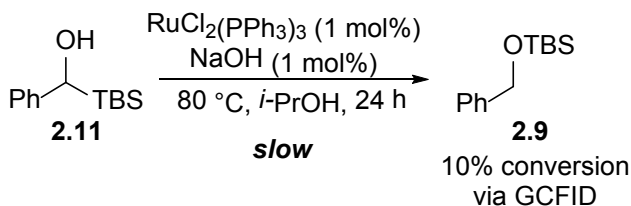
2.3.3. Control Experiments and Results

Preliminary experimentation was performed by Benjamin Reiner, an undergraduate member of the Byers laboratory. Upon treatment of aryl acylsilane **2.1** with 1 mol% of RuCl₂(PPh₃)₃ in isopropanol under an atmosphere of nitrogen, we were pleased to find formation of silyl ether **2.9** resulting from a Brook rearrangement as the major product of the reaction (**Scheme 2.6**). The reaction was monitored via GC in order to follow the consumption of aryl acylsilane **2.8** and formation of silyl ether **2.9**. Silyl ether **2.9** was isolated after purification via column chromatography in a 64% yield, and α -hydroxy silane **2.11** was isolated in a 14% yield. The other major by-product of the reaction was determined to be undesired TBS-silanol. The reaction with RuCl₂(PPh₃)₃ was very promising in demonstrating the first ruthenium-catalyzed Brook rearrangement, but there were other tests that needed to be performed before we could definitively conclude that the metal was involved in the rearrangement.



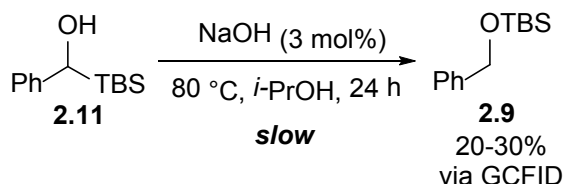
Scheme 2.6: Subjection of Acylsilane **2.8** to Catalytic Transfer Hydrogenation Conditions.

As mentioned in **Chapter 1**, it is known that α -hydroxy silanes can undergo the Brook rearrangement in the presence of catalytic amounts of base.³⁶ If the metal was simply hydrogenating acylsilane **2.8** to yield α -hydroxy silane **2.11**, sodium hydroxide could then catalyze the formation of silyl ether **2.9** through a Brook rearrangement. Independent synthesis of α -hydroxy silane **2.11** was achieved by subjecting aryl acylsilane **2.8** to DIBAL-H reduction in CH_2Cl_2 . In the presence of catalyst and base, α -hydroxy silane **2.11** did convert to silyl ether **2.9**, albeit very slowly (**Scheme 2.7**). Only about a 10% conversion to the silyl ether was found over the course of 24 h. This suggested that the rate of the reaction with acylsilane **2.8** was not in agreement with the measured rates of product formation with α -hydroxy silane **2.11** and was ruled out as a major contributor.



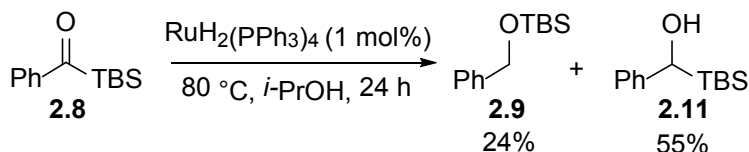
Scheme 2.7: Subjection of α -Hydroxy Silane **2.11** to Catalytic Transfer Hydrogenation Conditions.

Furthermore, in the presence of base alone, conversion of α -hydroxy silane **2.11** to silyl ether **2.9** was observed, but this was also found to be on a slower timescale than what was seen in the reaction of acylsilane **2.8** under the same conditions (**Scheme 2.8**). We were excited that the results with α -hydroxy silane **2.11** pointed towards a metal-mediated rearrangement.



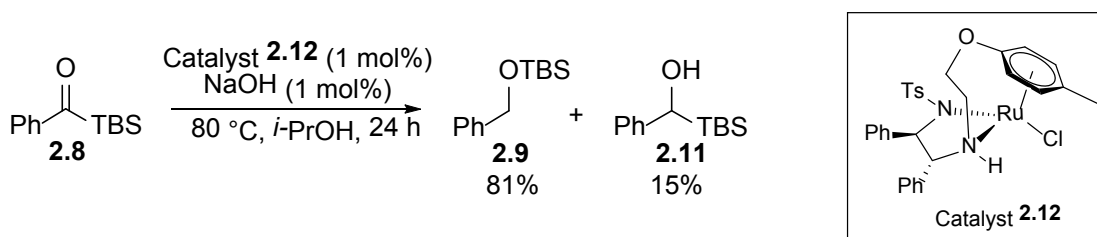
Scheme 2.8: Subjection of α -Hydroxy Silane **2.11** to Base.

Although the results from the control experiments were promising, more concrete findings came when we tested various ruthenium-hydrides in the absence of base. We picked different hydrides that we hypothesized might be the active form of the catalyst in the reaction outlined in **Scheme 2.6**. To our delight, upon reaction of acylsilane **2.8** with 1 mol% of $\text{RuH}_2(\text{PPh}_3)_4$ in the absence of base, silyl ether **2.9** was formed in a 24% yield (**Scheme 2.9**). However, the formation of silyl ether **2.9** did not prove that the ruthenium dihydride was the active catalyst, it only proved that ruthenium can catalyze the Brook rearrangement, which to our knowledge had not been previously reported in the literature.



Scheme 2.9: Subjection of Acylsilane **2.8** to Catalytic Transfer Hydrogenation Conditions without Base.

To examine the generality of a metal-catalyzed Brook rearrangement, we probed outer sphere catalysts in addition to those known to operate via the inner sphere process. Interestingly, a “Noyori-type” catalyst³⁷ with a proton donating ligand gave evidence of a Brook rearrangement. Upon subjection of acylsilane **2.8** to 1 mol% of catalyst **2.12**, silyl ether **2.9** was obtained in an 81% yield (**Scheme 2.10**). The outcome of the reaction was surprising to us because this catalyst is proposed to operate through an outer sphere mechanism. If this were the case, no Brook rearrangement would have occurred and only α -hydroxy silane **2.11** would have been detected in the reaction mixture. Nevertheless, the results provided evidence that the mechanism for this type of catalyst is step-wise, or asynchronous, instead of concerted, at least with acylsilanes. The results also support claims made by Ikariya and Dub as well as others that a solvent-mediated, stepwise process is the energetically preferred mechanism.³⁰



Scheme 2.10: Subjection of Acylsilane **2.8** to Catalytic Transfer Hydrogenation Conditions with an Outer Sphere Catalyst.

2.4 Conclusions

Our first goal involved testing various ruthenium catalysts in order to achieve a Brook rearrangement of aryl acylsilane **2.8**. The initial reaction that was tested with $\text{RuCl}_2(\text{PPh}_3)_3$ gave promising results, as a new silicon oxygen bond was formed in the

major product of the reaction, indicating that a Brook rearrangement had occurred. Control experiments were carried out and it was determined that the transition metal was catalyzing the rearrangement.

2.5 Experimental

2.5.1 General Information

General Procedures

Unless otherwise stated, all manipulations were carried out in oven-dried glassware under a nitrogen atmosphere using standard Schlenk line techniques.³⁸ Flash column chromatography, driven by compressed air, was performed with ZEOPrep 60 Eco 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using 250 μm Silica Gel 60 plates purchased from EMD Separations Technologies. TLC plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate or potassium permanganate stains.

Materials

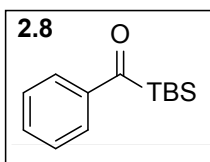
Solvents were used after passage through alumina columns under a blanket of argon and degassed *in vacuo*, except the following: isopropanol was refluxed over CaH_2 then distilled and degassed. All reagents were purchased from Sigma Aldrich and used as received except the following: benzaldehyde was purchased from Alfa Aesar, ruthenium catalysts were purchased from Strem Chemicals.

Instrumentation

^1H Nuclear Magnetic Resonance (NMR) spectra for characterization were recorded on a Varian VNMRs (500 MHz) or VNMRs (400 MHz) spectrometer. Chemical shifts are

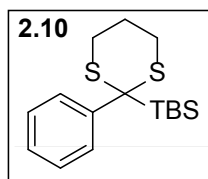
reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CHCl_3 : $\delta 7.26$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRs (125 MHz) or VNMRs (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl_3 : $\delta 77.16$). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility. Gas chromatograms (GC, GCMS) were obtained on a Shimadzu 2014 GCFID (Shimadzu SHRXI-5MS column, 15 m x 0.25 mm x 0.25 μm) and an Agilent 7820A GC/5975 MSD (Zebron ZB-5 column, 30 m x 0.25 mm x 0.25 μm) with the use of tetradecane or diglyme as internal standards.

2.5.2 Experimental Procedures and Characterization References

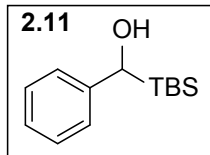


Synthesis of benzoyl-tert-butyldimethylsilane (2.8). To a 100 mL round-bottom flask was added 2-phenyl-2-trimethylsilyl-1,3-dithiane (1.24 g, 3.99 mmol, 1.00 equiv.) dissolved in acetone (10 mL) under ambient conditions. Chloramine-T (5.05 g, 22.2 mmol, 5.56 equiv.) dissolved in a 4:1 methanol:water mixture (25 mL) was added dropwise to the round bottom flask, which immediately turned the solution bright yellow. The mixture was then allowed to stir for 2 h open to air. The reaction was monitored via TLC (10% ethyl acetate/hexanes). The crude reaction mixture was concentrated via rotary evaporation then washed with brine

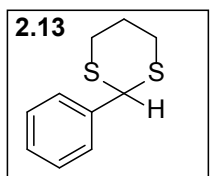
(75 mL) and saturated NaHCO_3 solutions (50 mL), and finally extracted with hexanes (3 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated via rotary evaporation. The crude reaction mixture was subjected to purification via column chromatography (1% ethyl acetate/hexanes) to yield a bright yellow oil (794 mg, 90.7%). Spectroscopic data were consistent with literature values.³⁹



Synthesis of 2-phenyl-2-tert-butyldimethylsilyl-1,3-dithiane (2.10). To an oven-dried 25 mL two-neck flask fitted with 180° joint was added 2-phenyl-1,3-dithiane (132 mg, 0.670 mmol, 1.00 equiv,) and in THF (2.6 mL). The solution was then cooled to -78°C and allowed to stir for 5 minutes. *n*-BuLi (0.36 mL, 0.81 mmol, 1.0 equiv.) was added drop-wise to the solution, which immediately turned a bright yellow, and allowed to stir for 2 h. *tert*-Butyldimethylsilyl chloride (121 mg, 0.805 mmol, 1.20 equiv.) was placed in an oven-dried 10 mL pear-shaped flask fitted with Claisen adaptor and dissolved in THF (2.2 mL) and was then cannula transferred to the round bottom flask. The solution was allowed to stir for 30 min at -78°C and then brought to ambient temperature and allowed to stir for 1.5 h. The reaction was monitored via TLC (5% ethyl acetate/hexane). The reaction mixture was quenched with saturated NH_4Cl solution (~20 mL) and extracted with diethyl ether. Solvents were removed by rotary evaporation and the crude reaction mixture was subjected to purification via column chromatography (5% ethyl acetate/hexanes) to yield a clear, colorless oil (187 mg, 90 %). Spectroscopic data were consistent with literature values.⁴⁰



Synthesis of (tert-butyldimethylsilyl)(phenyl)methanol (2.11). To an oven dried 100 mL round-bottom flask was added benzoyl-*tert*-butyldimethylsilane (309 mg, 0.983 mmol, 1.00 equiv.) dissolved in dichloromethane (2.5 mL), which was then cooled to $-78\text{ }^{\circ}\text{C}$ and allowed to stir for 5 minutes. DIBAL-H (1.46 mL, 1.67 mmol, 1.10) was added drop-wise to the flask and allowed to stir for 3 h. The reaction was then warmed to $0\text{ }^{\circ}\text{C}$ for 10 min and quenched with saturated aqueous sodium/potassium tartrate solution (90 mL). The solution was then warmed to ambient temperature and stirred for 1.25 h. Organic components were extracted with dichloromethane (3 x 100 mL) and the combined organic layers were dried over MgSO_4 and filtered. Solvent was removed via rotary evaporation to yield a pale yellow oil. The oil was subjected to purification via column chromatography (5% ethyl acetate/pentane) to yield a slightly yellow oil (278 mg, 90.1%). Spectroscopic data were consistent with literature values.⁴¹



Synthesis of 2-phenyl-1,3-dithiane (2.13). Benzaldehyde (9.95 g, 93.8 mmol, 1.00 equiv.), lithium bromide (2.02 g, 23.3 mmol, 0.250 equiv.) and 1,3-propanedithiol (10.1 mL, 101 mmol, 1.10 equiv.) were placed in a 500 mL two-neck round bottom flask and allowed to stir at $75\text{ }^{\circ}\text{C}$ for 3 h. The reaction was monitored via TLC (1:1 CH_2Cl_2 :hexanes). Upon completion, the reaction vessel was cooled to $0\text{ }^{\circ}\text{C}$ and diluted with CH_2Cl_2 (200 mL). The reaction mixture was then washed with a NaOH solution (10% w/v, 100 mL), brine (150 mL) and water (150 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated via rotary evaporation. The product was recrystallized from CH_2Cl_2 and hexane to give a

colorless solid (11.6 g, 63.5%), which was dried overnight over P_2O_5 and stored under nitrogen. Spectroscopic data were consistent with literature values.⁴²

Representative procedure for the Metal-Catalyzed Brook rearrangement of Acylsilane 2.1 to yield Silyl Ether 2.4. To an oven-dried 10 mL round-bottom flask fitted with 180° joint was added $RuCl_2(PPh_3)_3$ (2.4 mg, 3.7 mol, 0.020 equiv.). The flask was evacuated and backfilled three times with argon, and then isopropanol (1 mL, degassed) was added. The solution was then heated to 80 °C. To a separate oven-dried 10 mL pear-shaped flask fitted with Claisen adapter was added acylsilane **2.8** (42.1 mg, 0.191 mol, 1.00 equiv), which was evacuated and backfilled three times with argon and dissolved in isopropanol (1 mL, degassed). The solution containing acylsilane was transferred to the round-bottom flask via syringe. The pear-shaped flask was then rinsed with isopropanol (1.2 mL, degassed) and transferred to the round-bottom flask via syringe. To the flask was then added a solution of tetradecane in isopropanol (50 μ L, 61 mmol, 1.1 M, 0.30 equiv) as an internal standard and allowed to stir for 5 minutes. A 0 h time point aliquot of the bright yellow solution was taken before the addition of a NaOH solution in isopropanol (20 μ L, 3.9 mmol, 0.19 M, 0.02 equiv), which turned the solution a dark purple/brown and then amber in color as time progressed. Time points were taken at set intervals during the course of the reaction. After 46 h, the reaction mixture was concentrated via rotary evaporation and passed through a plug of silica gel (hexanes wash discarded and then collected 1:1 EtOAc:hexanes rinse) to yield silyl ether **2.2** as a slightly yellow oil (17 mg, 40%). Spectroscopic data were consistent with literature values.⁴³

2.6. References

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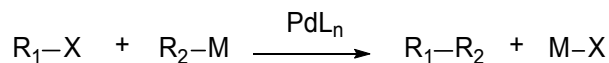
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CHAPTER 3

CATALYTIC INTERMOLECULAR CROSS COUPLING OF ARYL
ACYLSILANES AND ALDEHYDES

3.1 Introduction to Catalytic Cross Coupling

Catalytic cross coupling has gained wide-spread popularity as an efficient, atom-economical way to form new carbon-carbon bonds.⁴³ Although the term “cross coupling” is often used generally to describe two hydrocarbon fragments being joined with the assistance of a metal catalyst, the 2010 Nobel Prize in Chemistry described cross coupling more elegantly through the efforts put forth by the laboratories of Richard Heck, Ei-ichi Negishi and Akira Suzuki.⁴⁴ The catalytic cross coupling reaction with palladium species leads to the formation of a new C–C bond through oxidative addition, transmetalation, and reductive elimination (**Scheme 3.1**).^{43,45} For our purposes, cross coupling can be defined as the reaction of two molecules that would otherwise be unreactive towards each other through the formation of new carbon-carbon bonds with the assistance of a metal catalyst.



Scheme 3.1: General Motif of Coupling Chemistry Presented by the 2010 Nobel Prize in Chemistry Winners.

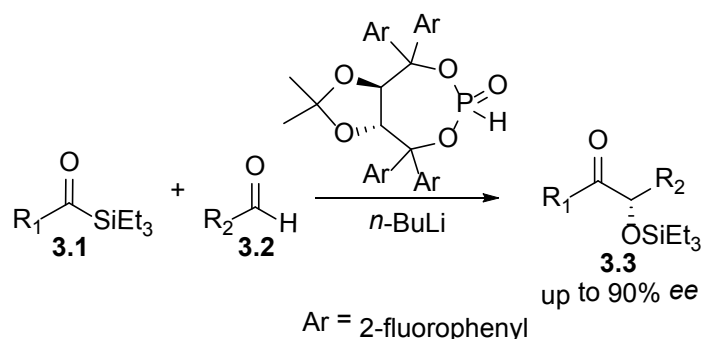
3.2 Catalytic Cross Coupling of Acylsilanes and Electrophiles

3.2.1 Acylsilanes and Aldehydes, Ketones, and Cyano-Esters

We began our investigation of the cross coupling with aldehydes due to the general availability of aldehydes, as well as literature precedents for their coupling capabilities with respect to acylsilanes. Jeffrey Johnson’s group has published work on this topic and other reactions involving acylsilane moieties, which was briefly outlined in

Chapter 1.¹⁷ His group has not only demonstrated catalytic cross coupling of acylsilanes and electrophiles, but also enantioselective routes with chiral metallophosphonate catalysts (**Scheme 3.2**).⁴⁶

As mentioned in **Chapter 1**, in 2004, Johnson's group demonstrated an enantioselective process with various metallophosphonate complexes derived from the TADDOL ligand in order to access enantio-enriched cross-silyl benzoin derivative **3.3**. It was found that the cross benzoin product could be obtained in good yields and high enantioselectivities with aryl acylsilane **3.1** and aldehyde **3.2** (**Scheme 3.2**).

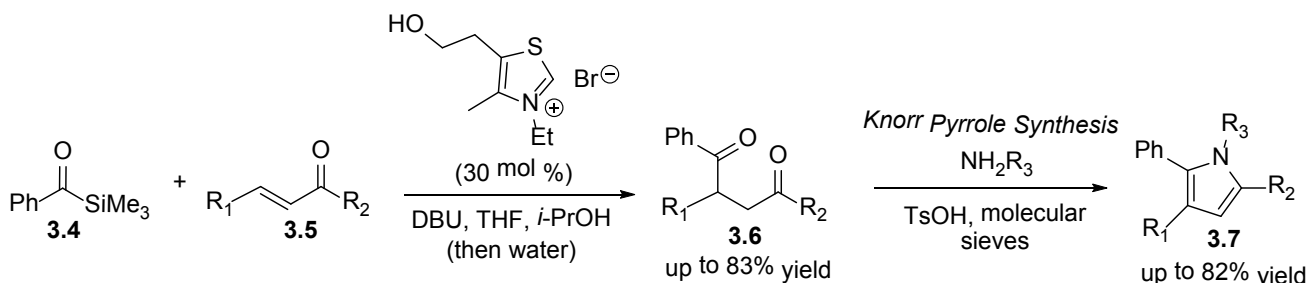


Scheme 3.2: Coupling of Acylsilanes and Aldehydes with Metallophosphonate Catalysts.

Although the Johnson chemistry has fundamentally demonstrated the cross coupling of acylsilanes with electrophilic partners, there are drawbacks to the above methodology. Not only is there a limitation in the types of electrophiles that can be implemented (only aldehydes and in some cases ketones), but there is also a limitation in oxidation state of the product (at least in the case of coupling of aldehydes with acylsilanes). Furthermore, most of his chemistry involves the use of cyanide-based

catalysts which can be toxic to handle as well as difficult to synthesize (see **Section 1.4.1**).

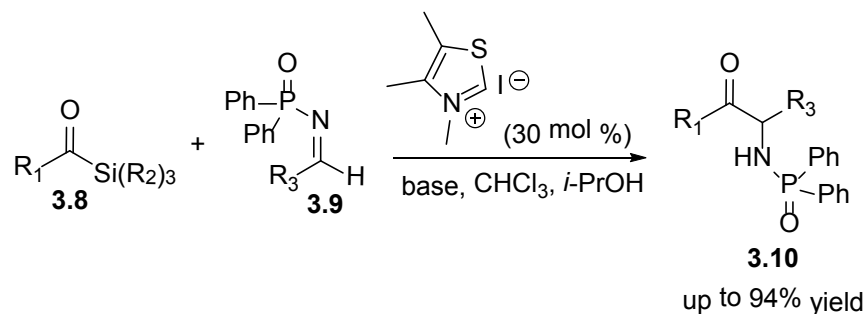
Apart from the Johnson group, a handful of other chemists have published work on the catalytic coupling of acylsilanes. Regarding acylsilanes and ketones, Karl Scheidt and co-workers have demonstrated a competent route to diketone analogs like **3.6**. In 2003, the Scheidt laboratory reported work on the catalytic reaction of acylsilane **3.4** and enone **3.5** via thiazolium-derived complexes to furnish substituted diketone **3.6** (**Scheme 3.3**).⁴⁷ Continued study and elaboration of the diketone products led to discovery of an efficient way to access highly-functionalized pyrrole **3.7** in good yields.



Scheme 3.3: Coupling of Acylsilanes and Enones with Thiazoliums.

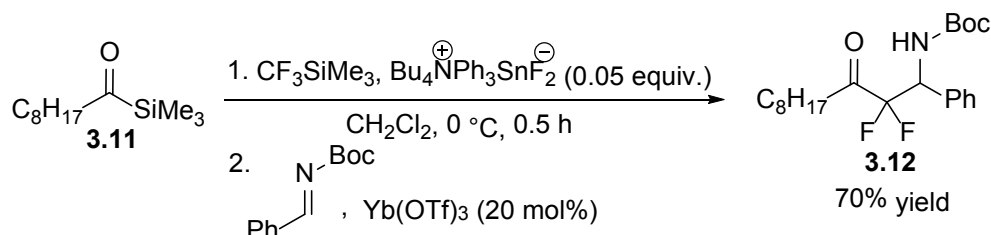
3.2.2 Acylsilanes and Imines

The coupling of acylsilanes with imines has been investigated to a lesser extent, but Scheidt's group has shown one example through the use of thiazolium-based catalysts. Upon treatment of acylsilane **3.8** with a phosphoryl-imine **3.9** in the presence of base (typically DBU), amino acid **3.10** was obtained in excellent yield (**Scheme 3.4**).⁴⁸ Both aryl and alkyl acylsilanes were tolerated, as well as substituted aryl and thiophenyl imines. To our knowledge, no asymmetric variant of this reaction has been reported.



Scheme 3.4: Coupling of Acylsilanes and Imines with Thiazoliums.

The other example of coupling acylsilanes and imines comes from Thierry Brigaud's group, who demonstrated the desired reactivity with the assistance of yttrium-based catalysts.⁴⁹ Subjection of acylsilane **3.11** to tin species followed by various aryl imines in the presence of catalytic amounts of Yb(OTf)₃, led to formation of fluorinated amino acid **3.12** in good yield (**Scheme 3.5**). The reaction works for both alkyl and aryl acylsilanes, although higher yields were obtained with the former.



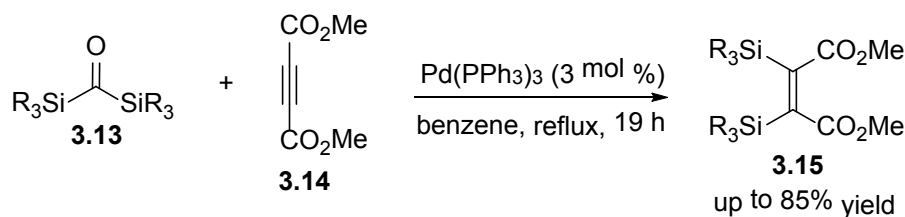
Scheme 3.5: Coupling of Acylsilanes and Imines with Ytterbium Catalysts.

3.2.3 Acylsilanes and Olefins and Alkynes

One of the unique aspects of employing a transition metal catalyst is that certain reactivity could potentially be accessed that would not be possible with other types of catalysts due to bonding through *d*-orbitals. Coupling of acylsilanes and olefins would be an example of a reaction that requires a transition metal catalyst. The following reports

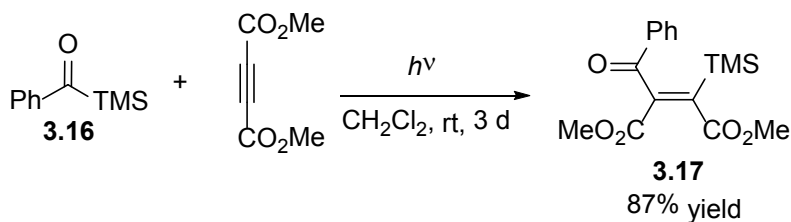
are, for the most part, examples of specific classes of olefins and alkynes (*i.e.* activated species) that can undergo coupling reactions. Ideally, our chemistry could be expanded upon to include coupling to many types of olefins and alkynes, in addition to more conventional electrophiles.

The first example comes from published work by Koichi Narasaka's group in 1996, in which bis(silyl) ketone **3.13** was coupled to substituted alkyne **3.14** in the presence of a palladium catalyst (**Scheme 3.6**).⁵⁰ The resulting bis(silyl) substituted olefin **3.15** was formed in an 85% yield after 19 h. Bis(silyl) ketone **3.13** can be readily accessed from bis(methylthio)methane and a variety of silyl groups can be employed in the transformation.



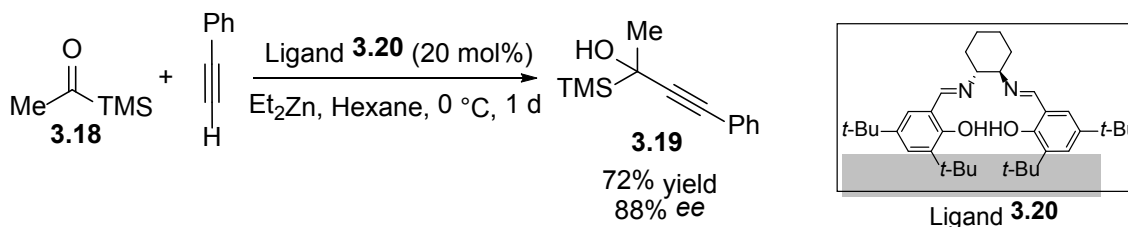
Scheme 3.6: Coupling of Acylsilanes and Alkynes with Palladium Catalysts.

In 2012, Carsten Bolm's laboratory also demonstrated coupling of acylsilanes with alkynes.⁵¹ Although the reported reaction is not catalytic, it is worth noting due to the fact that a retro-Brook rearrangement is proposed as part of the reaction mechanism. Aryl acylsilane **3.16** was added to dimethyl acetylenedicarboxylate after which irradiation was carried out with a fluorescent lamp (**Scheme 3.7**). The reaction allowed for access to substituted enone **3.17** in high yield.



Scheme 3.7: Photochemically-Induced Coupling of Acylsilanes and Alkynes.

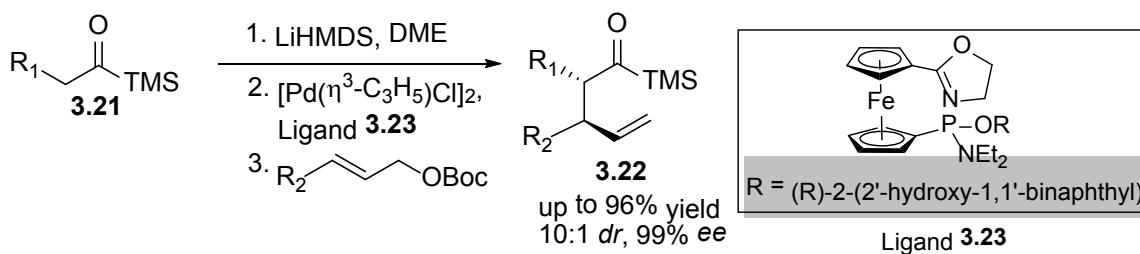
Terminal alkynes are also capable of undergoing a cross coupling reaction with acylsilanes as demonstrated by Gui Lu and Albert S. C. Chan in 2009 with copper and zinc based catalysts (**Scheme 3.8**).⁵² Methyl acylsilane **3.18** was coupled with ethynylbenzene to give chiral α -hydroxy silane **3.19** in good yield. Although the enantioselectivity was low with copper, using zinc-based complexes with various TADDOL-derived ligands led to the synthesis of α -hydroxy silanes in up to 88% *ee* and high yields.



Scheme 3.8: Coupling of Acylsilanes and Alkynes with Copper Catalysts.

To our knowledge, the only example of an acylsilane coupled to an olefin was published by Xue-Long Hao and co-workers and in 2010.⁵³ Upon addition of LiHMDS in the presence of a palladium catalyst and Boc-protected allyl species to acylsilane **3.21**, Hao's group found substituted acylsilane **3.22** could be accessed in high yield, good

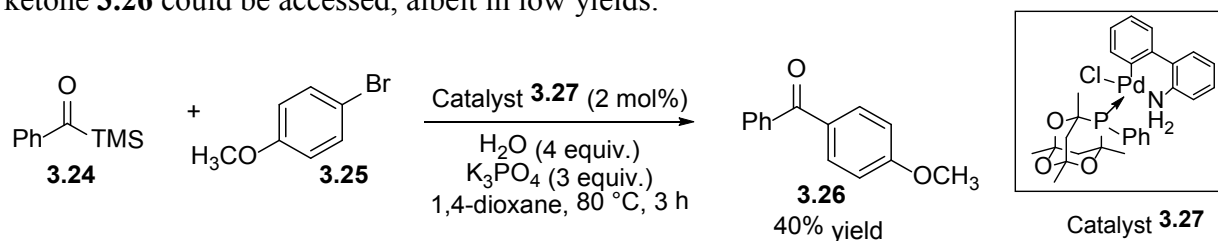
diastereoselectivity, and excellent enantioselectivity (**Scheme 3.9**). Other silyl groups were employed and gave good *anti* to *syn* selectivity.



Scheme 3.9: Coupling of Acylsilanes and Olefins with Palladium Catalysts.

3.2.4 Acylsilanes and Aryl Bromides and Allyl Species

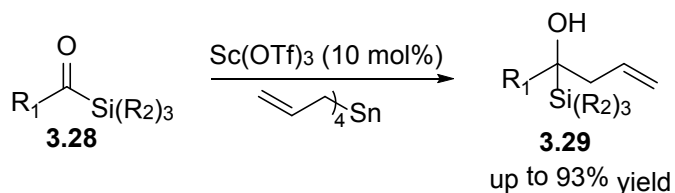
The last examples of catalytic coupling of acylsilanes and electrophiles come from the laboratories of Shane Krska, Bianca Flavia Bonini and Yasushi Tsuji. In 2011, Krska's group found that weakly bound silicon groups could be substituted by aryl substituents with the use of a palladium catalyst coordinated to a heteroatom-containing adamantyl ligand (**Scheme 3.10**).⁵⁴ Aryl acylsilane **3.24** was subjected to treatment with arylbromide **3.25** in the presence of palladium complexes, and it was found that simple ketone **3.26** could be accessed, albeit in low yields.



Scheme 3.10: Coupling of Acylsilanes and Aryl Bromides with Palladium Catalyst.

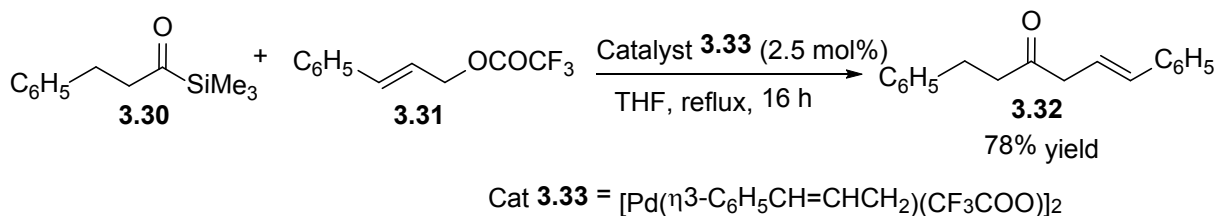
In 1998, Bonini and co-workers demonstrated a rare example of a tin allyl species reacting with acylsilane **3.28**, mediated by a scandium catalyst (**Scheme 3.11**).⁵⁵ The substituted α -hydroxy silane **3.29** that resulted was obtained in high yield. Both alkyl

and aryl acylsilanes were tolerated as well as various silicon groups; however trimethylsilyl acylsilanes gave the highest yields.



Scheme 3.11: Coupling of Acylsilanes and Tin-Allyls with Scandium Catalysts.

Since Bonini's work, an example of coupling of acylsilanes to activated allyl species was published in 2001. Tsuji and co-workers demonstrated that palladium catalysts were competent in the reaction of trimethylsilyl acylsilane **3.30** with disubstituted olefin **3.31** (Scheme 3.12).⁵⁶ This reaction led to formation of alkyl ketone **3.32** in good yields. The proposed mechanism involves a π -allyl intermediate formed through complexation of the olefin to the palladium catalyst which then reacts with the acylsilane.



Scheme 3.12: Coupling of Acylsilanes and Allyl Species with Palladium Catalysts.

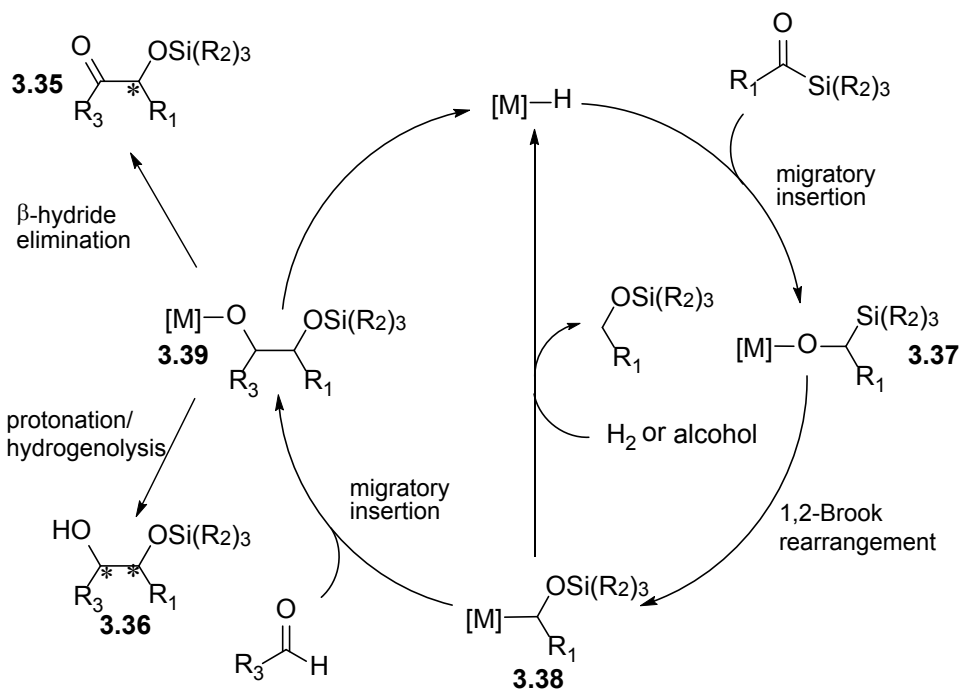
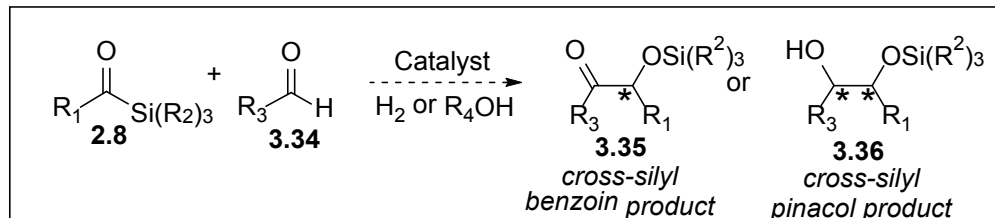
3.3 Efforts towards Ruthenium and Rhodium-Catalyzed Cross Coupling of Aryl

Acylsilanes and Aldehydes under Transfer Hydrogenation Conditions

3.3.1 Experimental Design and High-Throughput Screen

Prior to investigating the coupling capabilities of acylsilanes and electrophiles, procedural aspects of a large-scale screen had to be optimized. We decided to begin our screen with coupling of acylsilanes and aldehydes as described in **Section 3.2.1**. Aldehydes were chosen as capable coupling partners due to the fact that they are more electrophilic at the carbonyl carbon than ketones, which is where C–C bond formation was desired to occur. An aldehyde possessing an aryl substituent different from that of aryl acylsilane **2.8** was decided to be the substrate of choice so that detection of homocoupling versus the desired coupling would be more straight forward.

We envisioned the reaction mechanism proceeding through a metal-hydride inserting into acylsilane **2.4** in order to form metal-alkoxide **3.37**, which could then undergo a 1,2-Brook rearrangement (**Scheme 3.13**). The formation of the resulting metal-alkyl **3.38** is of paramount importance in the coupling chemistry, as the lifetime of this species must be long enough in order for the coupling partner to insert into the carbon-metal bond to form a new metal-alkoxide **3.39**. The alkoxide could then undergo β -hydride elimination to access the cross-silyl benzoin product **3.35**, in analogy to the Johnson chemistry (**Scheme 3.2**). If the reaction is carried out under reducing conditions, the resulting alkoxide **3.39** could undergo protonolysis/hydrogenolysis to yield the cross-silyl pinacol product **3.36**, which is not accessible through the Johnson protocol. The potential for accessing different product oxidation states through modification of the reaction conditions highlights the added utility of employing a transition metal catalyst.



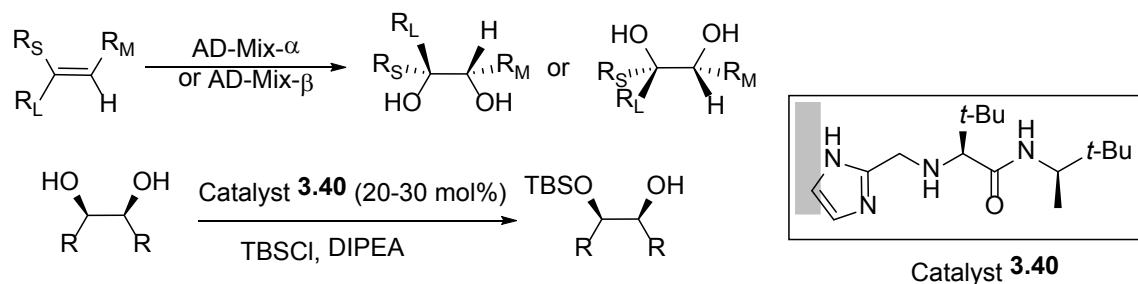
Scheme 3.13: Proposed Mechanistic Pathway for the Catalytic Coupling of Acylsilanes and Aldehydes.

The two proposed products of the reaction would be synthetically useful motifs that are not easily accessed. A similar oxidation pattern to the cross-silyl benzoin product **3.35** could be constructed from the benzoin condensation of two aldehydes in the presence of a catalytic amount of some nucleophile. The cross benzoin reaction has been widely used and studied,⁵⁷ and is sometimes catalyzed by some source of cyanide.⁵⁸ The propensity of the reaction to afford homocoupled products often requires the use of

aldehydes with significantly different electrophilicities, which limits the scope of the benzoin condensation. The proposed catalytic process in **Scheme 3.13** overcomes these setbacks while simultaneously protecting the resulting alcohol, which would allow for facile functionalization of the product.

As previously outlined, Jeffrey Johnson's group has provided a route to accessing the cross-silyl benzoin product **3.35** in an efficient manner, but this chemistry is limited to aldehyde and ketone coupling partners. A methodology that utilizes a transition metal catalyst would potentially allow for coupling of an assortment of electrophiles, such as olefins and alkynes. Additionally, modification of the reaction conditions allows access to different oxidation states of the product by slightly changing the reaction conditions.

One could envision the retro-synthesis of the other proposed product, the cross-silyl pinacol product **3.36**, starting with an olefin. Asymmetric dihydroxylation of olefins is one of the most popular and efficient routes to furnishing diols from tri-substituted olefins, but highly substituted olefins are not trivial to make (**Scheme 3.14**).⁵⁹ Furthermore, higher orders of substituted olefins do not react under the conditions. There are only a couple of reports of selective protection of diols, and there are limitations in terms of substrate scope (**Scheme 3.14**).⁶⁰ We have proposed a new way to access a mono-protected diol motif, whose chemoselectivity is dictated by judicious choice of aldehyde and acyl silane coupling partners.



Scheme 3.14: Synthetic Route to Furnishing Mono-Protected Diols.

After formulating the appropriate reaction conditions, a high-throughput screening process was developed in order to allow for multiple reactions to be carried out simultaneously. We proceeded to develop a multi-well, automated stirring and heating apparatus that could be put under an atmosphere of nitrogen or hydrogen. Fitted with aluminum blocks to seal the reaction vessels from air, the Advanced ChemTech LabmateTM proved to be a capable screening tool for the cross coupling reaction (**Figure 3.1**). The LabmateTM allowed for temperature screens, solvent screens and catalyst screens of up to 24 reactions at a time while allowing for time point aliquots to be taken. Once the initial reaction set-up was complete, minimal time was needed monitoring the gas flow and stir setting of the reaction apparatus.

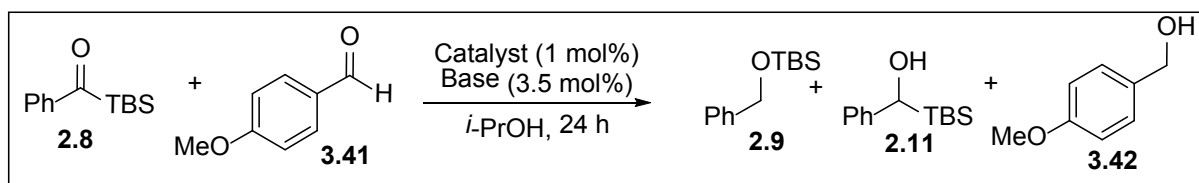


Figure 3.1: The Advanced ChemTech Labmate™ used in the Coupling Reactions.

3.3.2 Results

The first step in the screen was synthesizing various ruthenium catalysts and determining optimal reaction conditions. Synthesis of the ruthenium catalysts was carried out with the assistance of two undergraduates working on the project, Benjamin Reiner and Michael Wojnar. Phosphine, diamine, and BINAP/diamine⁶¹ ligated catalysts were synthesized in order to test a wide variety of catalyst classes (for a complete list of catalysts tested, refer to **Appendix 1**). The identity and amount of base was optimized prior to the large-scale screen and it was found that both NaOH and KOi-Pr showed higher activity over KOH and NaOi-Pr. In some cases, a co-solvent was introduced to increase solubility of the catalyst, however decreased reactivity was observed, perhaps due to solvent coordination to the metal center or due to the requirement for lower

reaction temperatures (based on the boiling point of the solvent). The four catalysts outlined in **Table 3.1**, are representative of the most active catalysts found during the course of the cross coupling reaction between acylsilane **2.8** and *p*-methoxy benzaldehyde **3.41**. The catalysts listed either showed evidence of silyl ether **2.9** resulting from a Brook rearrangement of acylsilane **2.8** (**Entries 1, 3**), or high activity for the hydrogenation of acylsilane **2.8** to α -hydroxy silane **2.11** and *p*-methoxy benzaldehyde **3.41** to *p*-methoxy benzyl alcohol **3.42** (**Entries 2, 4**).



Entry	Temp	Catalyst	Base	Conv. 2.8	Conv. 3.41	Yield 2.9	Yield 2.11	Yield 3.42
1 ^a	54 °C	3.43	KO <i>i</i> -Pr	50%	95%	15%	35%	90%
2	75 °C	RuCl ₂ (PPh ₃) ₃	KO <i>i</i> -Pr	71%	>95%	4%	60%	88%
3	75 °C	2.12	NaOH	95%	>95%	72%	3%	89%
4 ^a	54 °C	RhCl(PPh ₃) ₃	NaOH	95%	>95%	---	87%	91%

^a0.5 mL of methyl *t*-butyl ether added to catalyst for solubility purposes

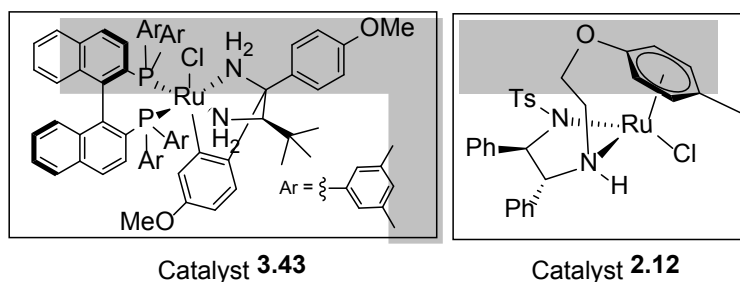


Table 3.1: Selected Coupling Reactions Demonstrating Highest Reactivity.

All attempts towards coupling of acylsilane **2.8** to aldehyde **3.41** utilizing different catalysts lead to no desired product. In all cases listed in **Table 3.1**, as well as

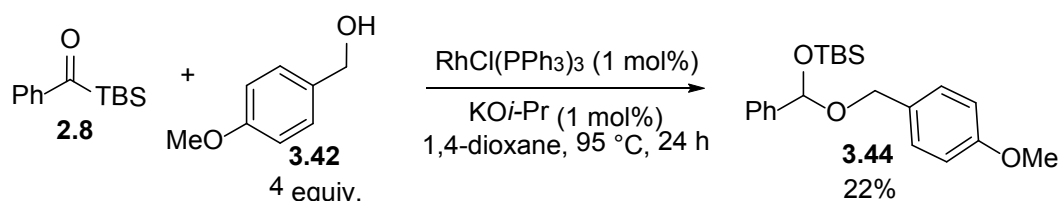
for many cases in the large-scale screen (see **Appendix 1**), reduction of aldehyde **3.41** to alcohol **3.42** was almost complete within the first hour of the reaction. The observation that aldehyde **3.41** was reduced so quickly potentially precluded the coupling reaction because there wasn't aldehyde present to form the desired C–C bond. On the other hand, if indeed the metal-alkyl **3.38** was being formed as outlined in **Scheme 3.31**, perhaps it was too short-lived to allow for insertion into even small quantities of aldehyde **3.41**. Protonolysis of metal-alkyl **3.38** would lead to formation of silyl ether **2.9**, which was observed in many of the reaction mixtures. Furthermore, increasing the ratio of aldehyde **3.41** to aryl acylsilane **2.8** did not seem to have any effect on the reaction outcome. Although no mechanistic experiments have been carried out in detail, one or both of the problems listed above could have lead to the lack of desired reactivity.

3.3.3 Discovery of a Novel Route to Silyl Ether Acetals under Transfer Hydrogenation Conditions

One of the ways in which we tried to overcome the problems described at the end of **Section 3.3.2** was by decreasing the amount of isopropanol in the reaction mixture, which we anticipated would decrease the amount of reduction of aldehyde **3.41**. We hypothesized this would help by lowering the number of reducing equivalents, which would in turn encourage the desired C–C bond formation instead of simply reducing the two species. Unfortunately, using solvent mixtures of isopropanol and various other solvents lead to decreased reactivity and no desired C–C bond formation. However, we proposed a different solution to our reactivity problem by employing the starting material as the reducing equivalent instead of isopropanol. We hypothesized that oxidation of

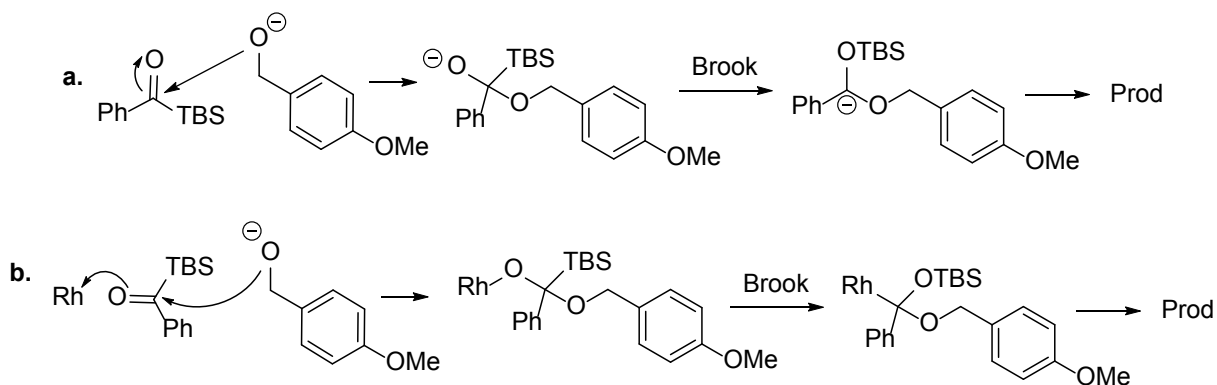
alcohol **3.42** to form the metal-hydride would lead to formation of aldehyde **3.41** *in-situ*, which would then undergo the desired transformation.

Wilkinson's catalyst⁶² was chosen for investigation of the above hypothesis due to its high activity for acylsilane reduction. Increasing the substrate concentration, as well as the equivalents of the alcohol lead to a new, higher-molecular weight product, which was determined by ¹H NMR to be acetal **3.44** (Scheme 3.15). Acetal **3.44** was the major product of the reaction, as determined by crude ¹H NMR and GCMS data and was isolated in a 22% yield, but not cleanly. Separation of the acetal from unreacted acylsilane proved extremely challenging, as the polarity of the two was very similar by TLC analysis and separation by distillation was ineffective.



Scheme 3.15: Synthesis of Silyl Ether Acetal **3.44**.

The mechanism for formation of acetal **3.44** remains unresolved and we are unsure of whether rhodium is actually involved in the Brook rearrangement under these conditions. Deprotonation of the alcohol could lead to nucleophilic attack on the acylsilane (Scheme 3.16a). A Brook rearrangement could then occur eventually leading to the product. However, complexation of the acylsilane to the metal through attack of the aldehyde could also occur. Then the acylsilane could undergo a Brook rearrangement facilitated by rhodium (Scheme 3.16b). Continued study of this reaction must be conducted in order to understand the unexpected outcome.



Scheme 3.15: Proposed Mechanisms for Formation of Acetal **3.44**.

3.4 Conclusions

The first attempts at cross coupling reactions of acylsilane **2.8** with aldehyde **3.41** were performed by a high-throughput screen of various ruthenium and rhodium catalysts. The reaction conditions were first optimized and the experimental set-up was developed to allow for the maximum number of reactions to be run at the same time. Unfortunately, the desired C–C bond formation was not observed due to several challenges: either reduction of aldehyde **3.41** was too fast, and/or the lifetime of the proposed metal-alkyl was too short in order for the insertion of aldehyde **3.41** to occur.

In an attempt to overcome the problems associated with the coupling reaction between acyl silanes and aldehydes, we hypothesized that decreasing the amount of isopropanol would lead to a higher concentration of aldehyde **3.41**. This hypothesis was tested by replacing aldehyde **3.41** with alcohol **3.42** and eliminating the use of isopropanol. Although we were still operating under transfer hydrogenation conditions, alcohol **3.42** was employed as the reducing equivalent to form the metal-hydride, which

would ensure formation of aldehyde **3.41**. However this lead to formation of an unexpected species, acetal **3.44** in which C–O bond formation occurred preferentially over C–C bond formation.

3.5 Experimental

3.5.1 General Information

General Procedures

Unless otherwise stated, all manipulations were carried out in oven-dried glassware under a nitrogen atmosphere using standard Schlenk line techniques in combination with the Advanced ChemTech LabmateTM.³⁶ Flash column chromatography, driven by compressed air, was performed with ZEOPrep 60 Eco 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using 250 μm Silica Gel 60 plates purchased from EMD Separations Technologies. TLC plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate or potassium permanganate stains.

Materials

Solvents were used after passage through alumina columns under a blanket of argon and degassed *in vacuo*, except the following: isopropanol was refluxed over CaH_2 then distilled and degassed, 1,4-dioxane was distilled and degassed, benzyl alcohol, *p*-methoxy benzyl alcohol, and methyl *t*-butyl ether were degassed. NaOi-Pr and KOi-Pr were synthesized according to literature procedure and stored in the glovebox under a nitrogen atmosphere.⁶³

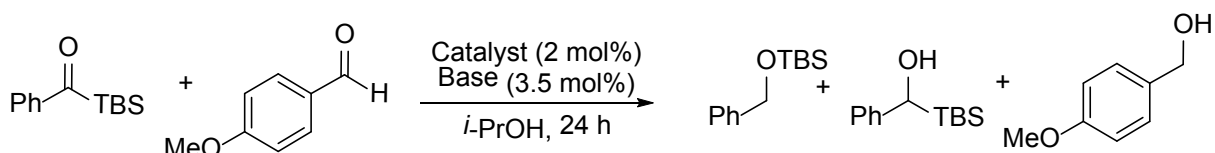
Metal Catalysts. $\text{RuH}_2(\text{PPh}_3)_3$ was purchased from Aldrich. N-[(1S,2S)-1,2-Diphenyl-2-(2-(4-methylbenzyloxy)ethylamino)-ethyl]-4-methylbenzene sulfonamide(chloro)ruthenium(II) (S,S)-Ts-DENEB (**2.12**), chloro{(R)-(+)-2,2'-bis[di(3,5-xyllyl)phosphino]-1,1'-binaphthyl}[(2R)-(-)-1-(4-methoxyphenyl)-1-(4-methoxyphenyl-kC)-3-methyl-1,2-butanediamine]ruthenium(II) (**3.43**), $\text{RuCl}[(\text{R})\text{-daipena}][(\text{R})\text{-xylbinap}]$, $\{[(1\text{R},2\text{R})\text{-2-amino-1,2-diphenylethyl}](4\text{-toluenesulfonyl)amido}\}(\text{p-cymene})(\text{pyridine})\text{ruthenium(II)}$ tetrafluoroborate, $\text{RuCl}_2(\text{PPh}_3)_3$ and $\text{RuHCl}(\text{PPh}_3)\text{CO}$ were purchased from Strem Chemicals. $\text{RhCl}(\text{PPh}_3)_3$ was purchased from Acros Chemicals. $\text{RuCl}_2[(\text{R})\text{-tolbinap}](\text{pica})$ was synthesized according to patent procedure.⁶⁴ $\text{RuCl}_2(\text{dppe})_2$, $\text{RuCl}_2(\text{Pt-Bu}_3)_3$, $\text{RuCl}_2(\text{PCy}_3)_3$, $\text{RuCl}_2(\text{dcpe})_2$, $\text{RuClH}(\text{PPh}_3)_4$ were synthesized by Benjamin Reiner according to literature procedure.⁶⁵ $\text{RuCl}(\text{cymene})(\text{Ts-diaminoethane})$ was synthesized by Michael Wojnar according to literature procedure.⁶⁶

Instrumentation

^1H Nuclear Magnetic Resonance (NMR) spectra for characterization were recorded on a Varian VNMRS (500 MHz) or VNMRS (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CHCl_3 : $\delta 7.26$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRS (125 MHz) or VNMRS (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl_3 : $\delta 77.16$). High-

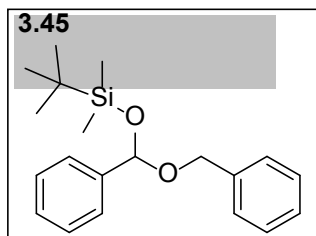
resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility. Gas chromatograms (GC, GCMS) were obtained on a Shimadzu 2014 GCFID (Shimadzu SHRXI-5MS column, 15 m x 0.25 mm x 0.25 μ m) and an Agilent 7820A GC/5975 MSD (Zebron ZB-5 column, 30 m x 0.25 mm x 0.25 μ m) with the use of tetradecane or diglyme as internal standards.

3.5.2 Experimental Procedures and Characterization Data



Representative Procedure for the Cross Coupling of Acylsilane 2.8 with p-Methoxy Benzaldehyde 3.41 Employing the Advanced ChemTech Labmate™. To a 25 mL pear shaped flask fitted with Claisen adapter was added benzoyl *tert*-butyl dimethyl silane (200 mg, 0.907 mmol, 1.00 equiv.) which was evacuated and backfilled with argon three times. To the flask was added *p*-methoxy benzaldehyde (110 μ L, 0.907 mmol, 1.00 equiv.), diglyme (636 μ L, 4.44 mmol, 4.89 equiv.) and isopropanol (15 mL) to achieve a 0.06M solution. The solution was allowed to stir for 5 minutes at room temperature before a zero hour aliquot was taken. To a series of four 7 mL scintillation vials was added equal amounts of $\text{RuCl}_2(\text{PPh}_3)_3$ (2.2 mg, 0.0023 mmol, 0.020 equiv) which were then fitted on the Labmate™ with sealed aluminum blocks and purged with argon for approximately 5 minutes. The acyl silane/aldehyde solution was then transferred via syringe evenly among the four vials and allowed to stir at room temperature for 5

minutes. A 0.06M solution of KOiPr in isopropanol (127 μ L, 0.00794 mmol, 0.0350 equiv.) was then added to each vial, heated to 80 $^{\circ}$ C and allowed to stir for 24 h. 1 h and 24 h time points were taken and analyzed via GCFID.



Synthesis of ((benzyloxy)(phenyl)methoxy)(tert-butyl)dimethylsilane 3.45. To an oven-dried 10 mL pear-shaped flask fitted with Claisen adaptor was added benzoyl *tert*-butyl dimethyl silane (100 mg, 0.454 mmol, 1.00 equiv.),

which was evacuated and backfilled with argon three times on a Schlenk line. To the flask was added 1,4 dioxane (1.8 mL), diglyme (500 μ L, 1.75 mmol, 3.80 equiv.), which was allowed to stir at ambient temperature for 5 minutes. To a separate oven-dried 10 mL pear-shaped flask fitted with 180 $^{\circ}$ joint was added KOi-Pr (0.4 mg, 0.004 mmol, 0.01 equiv.) in the glovebox, which was then brought out and briefly opened to add RhCl(PPh₃)₃ (46 mg, 0.0050 mmol, 0.010 equiv.). The flask containing base and catalyst was then evacuated and backfilled with three times with argon on the Schlenk-line. To the flask containing base and catalyst was then added benzyl alcohol (224 μ L, 1.81 mmol, 4.00 equiv.). The solution of acylsilane, diglyme and solvent was then transferred via syringe to the flask containing base, catalyst, and alcohol. The bright yellow mixture was heated to 95 $^{\circ}$ C and stirred for 5 minutes before a 0 hr time point was taken. The reaction mixture turned an orange/red within 1 hr and then more brown/green as time progressed. After 62 hrs, the reaction was stopped and excess benzyl alcohol was removed via K \ddot{u} gelrohr distillation. Purification by column chromatography (1% Et₃N and 1% EtOAc in hexanes v/v) delivered the title compound as a clear, colorless oil (90%

pure, 32 mg, 22%) which was structurally elucidated via preliminary ^1H and ^{13}C NMR analysis. No IR or mass spec data were obtained.

$R_f = 0.36$ (1% Et_3N and 1% EtOAc in hexanes v/v/v); ^1H NMR (500 MHz, CDCl_3) δ 7.48 – 7.42 (m, 2H), 7.36 – 7.17 (m, 8H), 5.88 (s, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.43 (d, $J = 11.7$ Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), -0.00 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 141.20, 138.54, 128.43, 128.30, 127.86, 127.74, 127.51, 127.04, 126.63, 96.66, 67.19, 66.26, 25.94, 25.80, 18.39, -4.25, -4.70.

3.5.3. NMR Spectral Data

Figure 3.2: ^1H NMR of Silyl Ether Acetal (3.45)

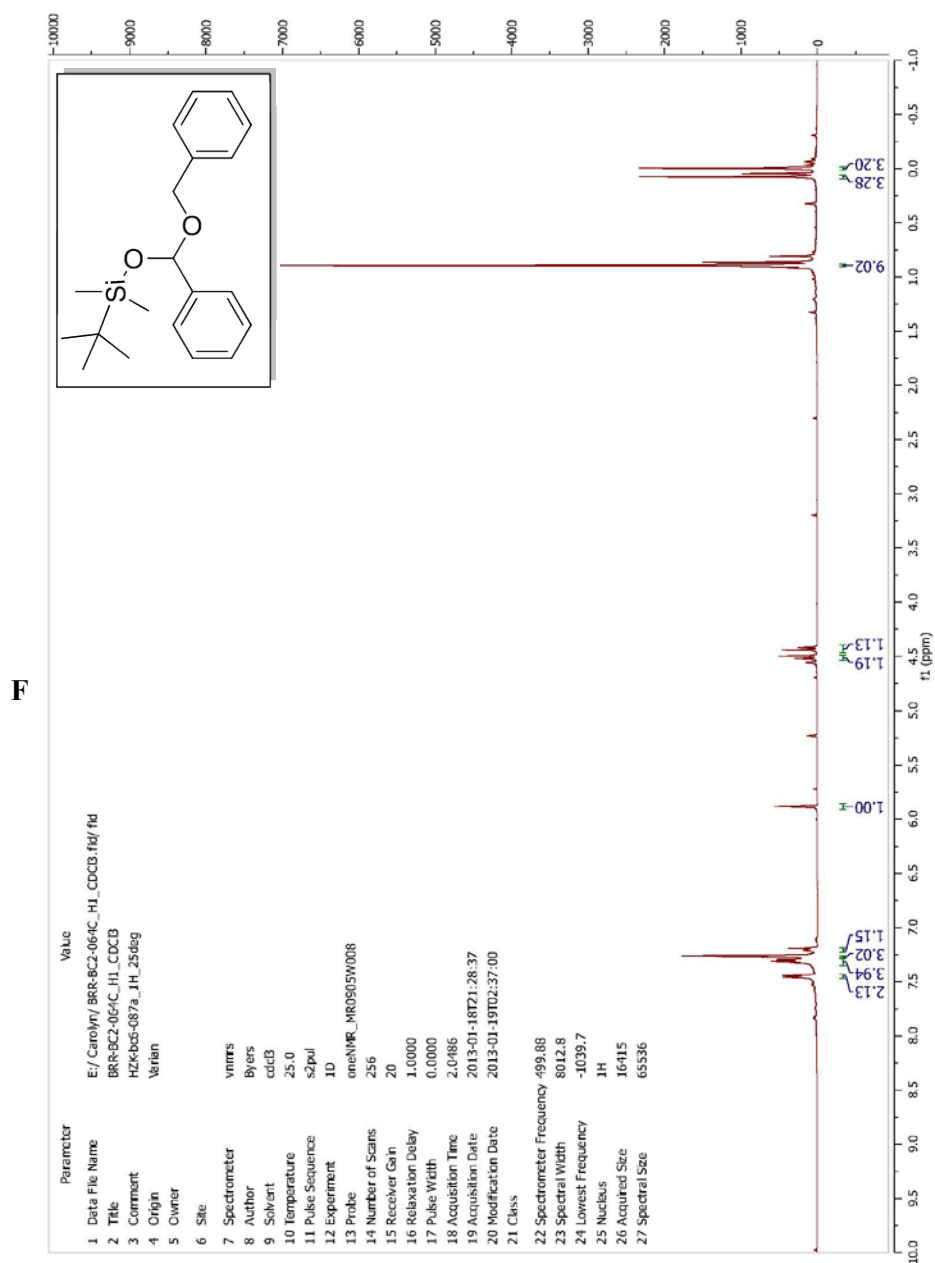
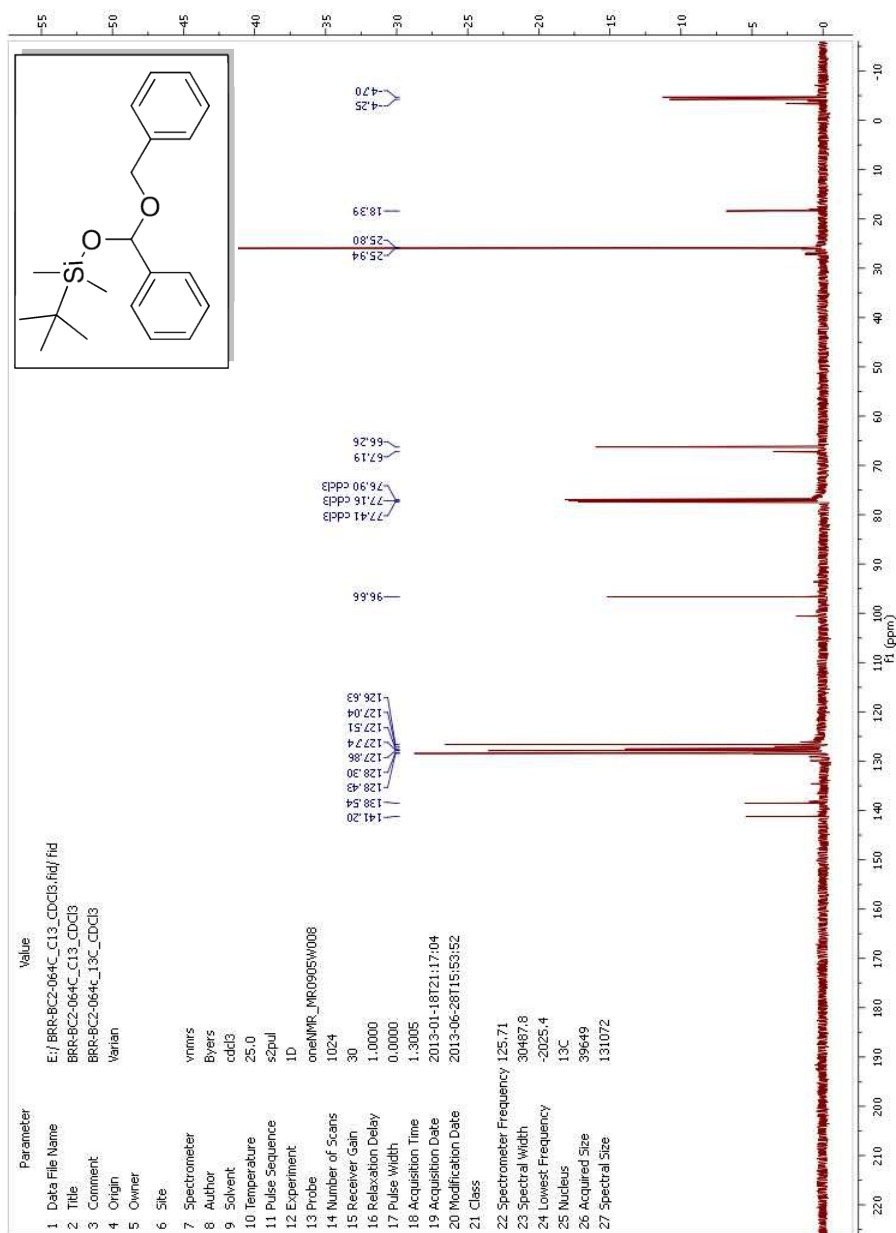


Figure 3.3: ^{13}C NMR of Silyl Ether Acetal (3.45)

3.6. References

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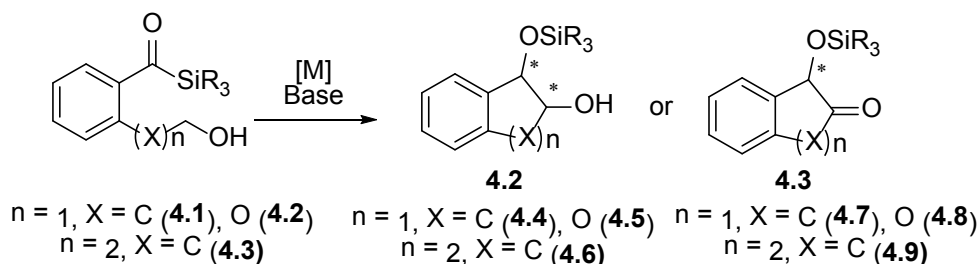
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CHAPTER 4
CATALYTIC INTRAMOLECULAR CROSS COUPLING OF ARYL
ACYLSILANES AND ALDEHYDES

4.1 Introduction

As outlined in Chapter 3, there are a handful of examples of catalytic intermolecular reactions of acylsilanes. There are far fewer examples, however of catalytic intramolecular reactions of acylsilanes.⁶⁷ An intramolecular reaction is more entropically favorable than an intermolecular reaction, making it a more feasible option to achieve the desired reactivity we sought to accomplish. With an entropic advantage, the coupling of an aldehyde to an acylsilane could be accomplished by tethering both to the same molecule. The substrate design for such a reaction was simple in theory, but proved to be more difficult to synthesize than anticipated due to various road blocks we came across in testing of different routes. It was determined that generating the free aldehyde might be too unstable and would undergo facile reduction under the reaction conditions. Thus, we decided to generate the aldehyde *in situ* in a similar fashion to the reaction shown in **Scheme 3.15**, in which the starting material is used as the reducing equivalent (**Scheme 4.1**). Success was met when the novel acylsilane was synthesized in five steps based on published work by Carsten Bolm's laboratory in 2012.^{67b}

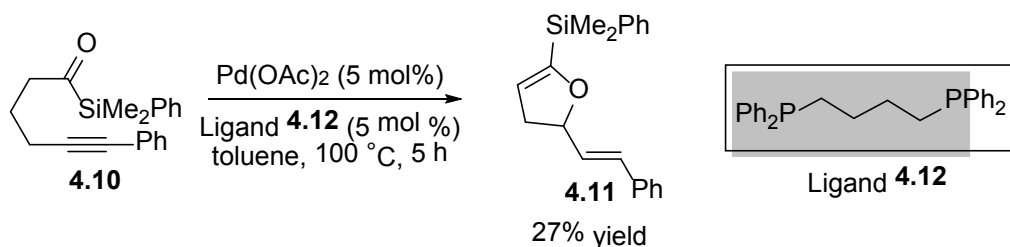
The intramolecular coupling chemistry has yet to be tested, but we envisioned the substrate undergoing a catalytic transfer hydrogenation reaction (**Scheme 4.1**). This would lead to the formation of substituted heteroatom-containing bicyclic compounds through an *in-situ* generation of the aldehyde coupling partner. Our novel strategy would allow access to bicyclic motifs **4.2** or **4.3** in a highly efficient, atom-economical manner. The reaction conditions will be described in greater detail in section **4.3**.



Scheme 4.1: The Proposed Intramolecular Cross Coupling of Acylsilanes and *in situ* Generated Aldehydes.

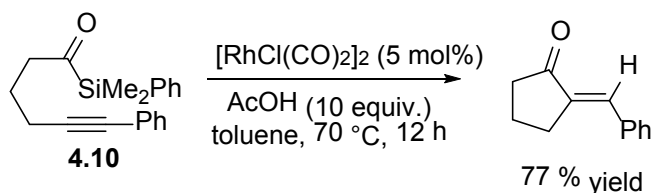
4.2 Intramolecular Cross Coupling of Acylsilanes and Alkynes

As previously mentioned, we envisioned the coupling of acylsilanes to aldehydes in an intramolecular reaction. However, the only known examples of this type of transformation involve coupling of acylsilanes and alkynes. In 2001, Koichi Narasaka's group demonstrated an intramolecular reaction of acylsilanes and alkynes (**Scheme 4.2 and 4.3**) which expanded upon an intermolecular variant published earlier in his laboratory.^{67a} His group employed both palladium as well as rhodium catalysts to facilitate an intramolecular cross coupling to access two different and synthetically useful products. In the presence of a palladium acetate catalyst, acylsilane **4.10** was shown to undergo the intramolecular coupling reaction to yield cyclic vinyl ether **4.11** in a 27% yield (**Scheme 4.2**). However, the vinyl ether product was not the desired product of the reaction, thus they continued their studies with other catalysts.



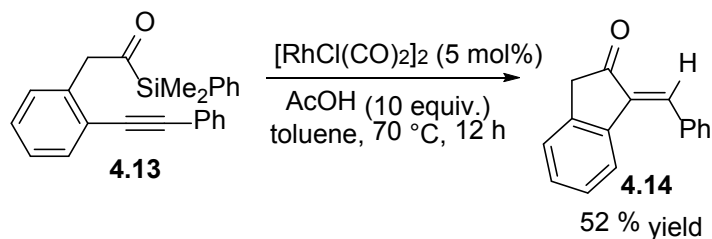
Scheme 4.2: The Intramolecular Cross Coupling of Acylsilanes and Alkynes with Palladium Catalysts.

Upon further investigation, they found that rhodium catalyzed the intramolecular cross coupling of the same acylsilane in the presence of an acid additive, which afforded 2-benzylidene cyclohexanone in a 77% yield (**Scheme 4.3**). The acid additive lead to higher yields because it was proposed that the product was released via protonation in the last step of the catalytic cycle by a small amount of water in the reaction mixture.



Scheme 4.3: The Intramolecular Cross Coupling of Acylsilanes and Alkynes with Rhodium Catalysts.

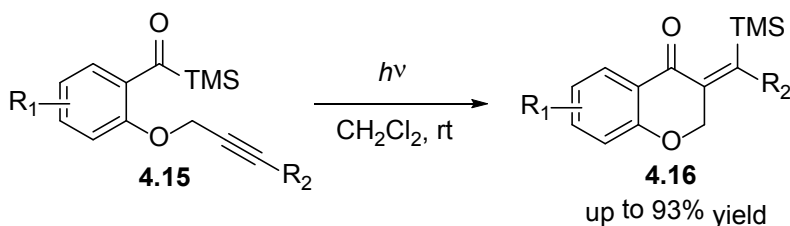
Other acylsilane substrates were synthesized and tested under the reaction conditions, but only acylsilane **4.13** gave an acceptable yield of the cyclopentanone product **4.14** (**Scheme 4.4**). The examples from Narasaka's group set the stage for coupling of acylsilanes to "non-traditional" electrophiles, such as alkynes with the assistance of a transition metal catalyst.



Scheme 4.4: The Intramolecular Cross Coupling of Acylsilanes and Alkynes with Rhodium Catalysts.

The most relevant example of intramolecular coupling, however, comes from Carsten Bolm's group.^{67b} His paper published in mid-2012 gave us insight into the synthetic route to access a novel acylsilane. As mentioned in section 3.2.3, Bolm's group first demonstrated an intermolecular coupling of aryl acylsilanes with alkynes through photochemical excitation (**Scheme 4.5**). Without the use of a metal catalyst, the intramolecular coupling was achieved in an environmentally friendly manner and in excellent yield.

Upon subjection of aryl acylsilane **4.15** to UV light, an intramolecular reaction of the acylsilane with the substituted alkyne occurred leading to formation of chromone **4.16** in excellent yield in most cases (**Scheme 4.5**). A handful of substrates with substitution on the phenyl ring were tolerated in the reaction and cleanly converted to the bicyclic product. One of the few limitations found was that a terminal alkyne was not tolerated as this lead to no formation of the expected product.

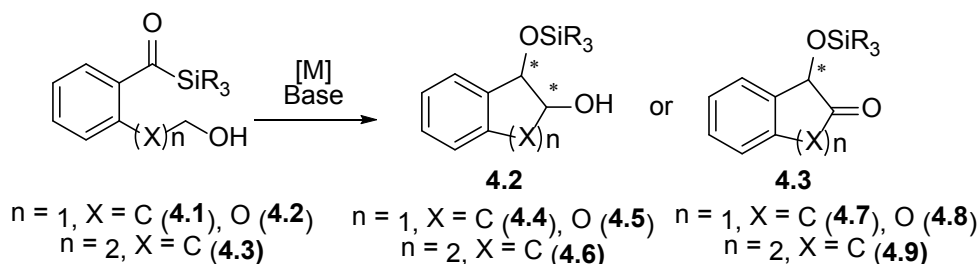


Scheme 4.5: The Intramolecular Cross Coupling of Acylsilanes and Alkynes Induced by Photochemical Irradiation.

The work by Bolm's group was instrumental in our synthetic route to a novel acylsilane because he had reported the synthesis of an intermediate that was similar to one we proposed for our own substrate. The synthesis of Bolm's acylsilane substrates was reported in a straight-forward, fairly high-yielding manner with known reagents and conditions. Our institution of Bolm's synthesis will be outlined in more detail in the next section.

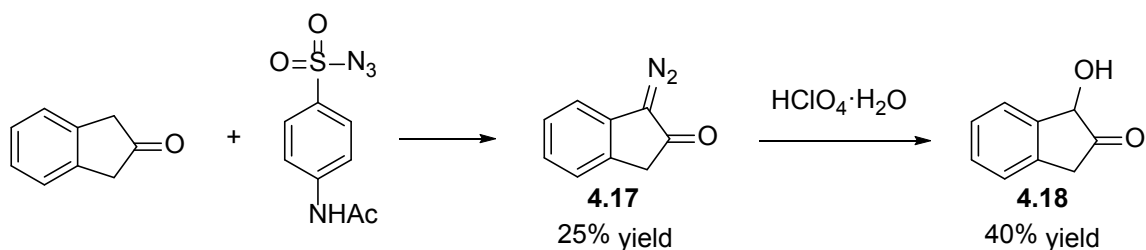
4.3 Experimental Design and Synthesis of a Novel Acyl Silane

Acylsilane **4.1** containing an alcohol moiety was proposed as the first substrate to target in the intramolecular cross coupling of acylsilanes and aldehydes (**Scheme 4.6**). Cross coupling of acylsilane **4.1** would allow for an atom-economical route to the oxygenated bicyclic compounds. After much effort was given towards the synthesis of acylsilane **4.1**, we encountered difficulty in deprotonation of the dithiane proton and subsequent silylation. Due to the unforeseen obstacles, we turned to another substrate design. Based on the synthesis by Bolm's group, we envisioned accessing acylsilane **4.2** with slightly different electronic properties through the installation of an ether tether. To our knowledge, all substrates shown in **Scheme 4.6** have never been synthesized before.



Scheme 4.6: The Proposed Intramolecular Cross Coupling of Acylsilanes and *in situ* Generated Aldehydes.

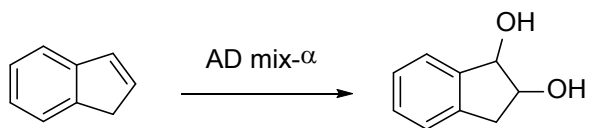
Bicyclic moieties containing the type of oxygenation pattern shown are difficult to access via alternative routes. One known route to accessing oxygenated bicyclic compounds begins with commercially available 1,2-indanedione, although this route is low yielding (**Scheme 4.7**).⁶⁸ Treatment of the indanedione with 4-acetamidobenzenesulfonyl azide generates diazo **4.17**. Then subjection of **4.17** to perchloric acid furnishes the bicyclic indenone **4.18** as a mixture of enantiomers. Protection would be necessary if further functionalization was desired.



Scheme 4.7: Alternative Route to Accessing a Similar Motif to Coupling Product **4.7**.

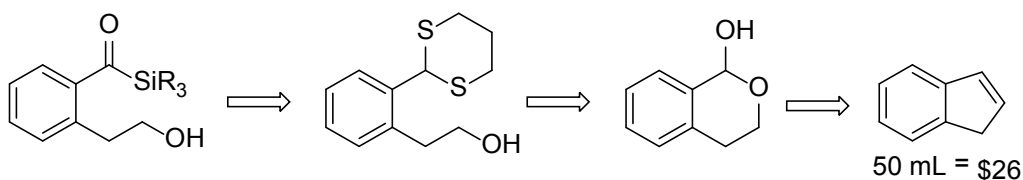
On the other hand, bicyclic diol **4.4** could be accessed via asymmetric dihydroxylation of indene (**Scheme 4.8**).⁶⁹ However, as previously mentioned there are a limited number of ways to selectively protect one alcohol over the other. The limitation

described hinders further functionalization of one alcohol moiety and thus limits the application of the route.



Scheme 4.8: Alternative Route to Accessing a Similar Motif to Coupling Product **4.4**.

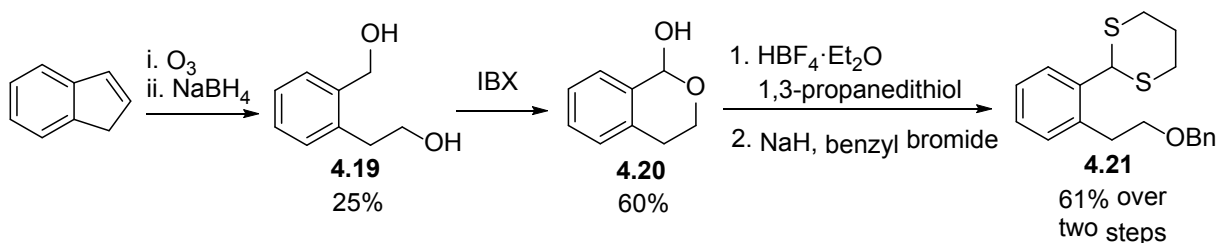
4.3.1. Efforts Towards the Synthesis of a Novel Acylsilane



Scheme 4.9: Retrosynthesis of Substrate **4.1**.

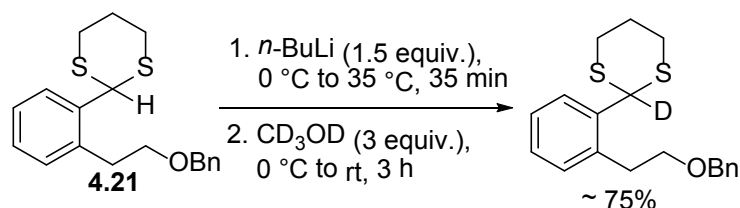
The synthesis of acylsilane **4.1** began fairly smoothly, but proved more difficult than anticipated. The retrosynthesis outlined in **Scheme 4.9** details the formation of dithiane intermediates similar to the synthesis of acylsilane **2.1**, which we believed could be accessed from indene through a seven-step procedure. In the forward direction, ozonolysis of indene under reducing conditions led to diol **4.19**, although this reaction was not optimized (**Scheme 4.10**). The reaction was found to be sensitive to the amount of sodium borohydride added and in some cases full conversion to the diol was not accomplished. However, upon subjection of diol **4.19** to 2-iodoxybenzoic acid, the bicyclic lactol **4.20** was readily accessed in a 60% yield. Over-oxidation of the lactol to the lactone was problematic in this step, but the two products were separated from one another by column chromatography. Opening of lactol **4.20** with 1,3-propanedithiol lead

to the free alcohol, which upon esterification with benzyl bromide readily afforded dithiane **4.21** in a 61% yield over two steps.

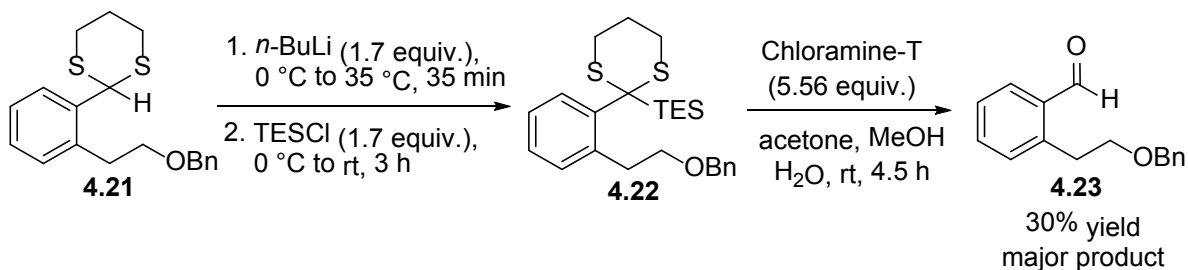


Scheme 4.10: Synthesis of Dithiane Intermediate **4.21**.

The most challenging aspect of the sequence was the next two steps in which deprotonation of the dithiane proton followed by silylation seemed to be thwarted by unforeseen steric and/or energetic hindrance. Deuterium labeling experiments in which deprotonation with 1.5 equivalents of *n*-BuLi at -78°C and then allowing the reaction to warm up, followed by addition of deuterated methanol gave evidence of significant deuterium incorporation on the dithiane carbon (**Scheme 4.11**). However, these conditions were much harsher than preliminary conditions, which proved that deprotonation of the dithiane proton was not as energetically accessible. Upon silylation with TESCl, silylated dithiane **4.22** was obtained, however purification proved challenging as unreacted starting material was not easily separated from the mixture and resubjection of the material to the reaction conditions was not attempted (**Scheme 4.12**). Unfortunately, the only attempted oxidation of dithiane **4.22** to the acylsilane lead to desilylation of the acylsilane, which hinted that the triethylsilyl group might have been too labile. Other oxidation conditions, *i.e.* in the absence of protic solvents, were not tested, however the route remains a viable option to the desired substrate.

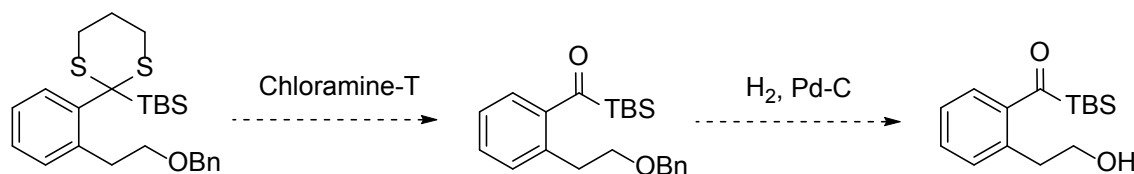


Scheme 4.11: Deuterium Experiment with CD_3OD to test Deprotonation of Dithiane **4.21**



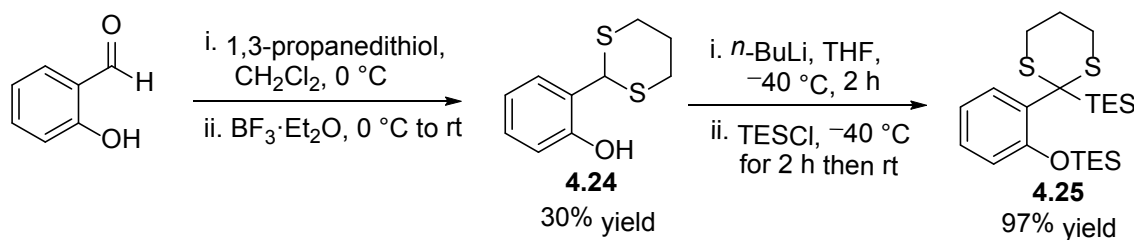
Scheme 4.12: Undesired Synthesis of Aldehyde **4.23**.

Although incomplete, this route remains a viable option to synthesizing the desired substrate and perhaps using a more bulky silyl group, such as *tert*-butyldimethyl silane or aprotic solvents, would allow for oxidation to the acylsilane with chloramine-T (**Scheme 4.13**). Other oxidation conditions could also be tested, such as using NBS in a similar fashion to the synthesis of acylsilane **4.2** outlined below. The last step would be deprotection of the alcohol, which we had hypothesized would be viable by hydrogenolysis using palladium on carbon under an atmosphere of H_2 . Preliminary testing of the acylsilane **2.8** under hydrogenation conditions with palladium on carbon gave evidence that the acylsilane moiety remained intact, and would be unreactive for the final transformation.



Scheme 4.13: Proposed End Game to Furnish Acylsilane **4.1**.

The work put forth by Bolm's group showed an alternative route to accessing a similar substrate to the carbocyclic substrate. Following his procedure, subjection of commercially available and inexpensive salicylaldehyde to dithiane protection with 1,3-propanedithiol lead to formation of free phenol dithiane **4.24** (**Scheme 4.14**).^{67b} A double deprotonation with *n*-BuLi followed by silylation with TESCl afforded silylated dithiane **4.25** in excellent yield.

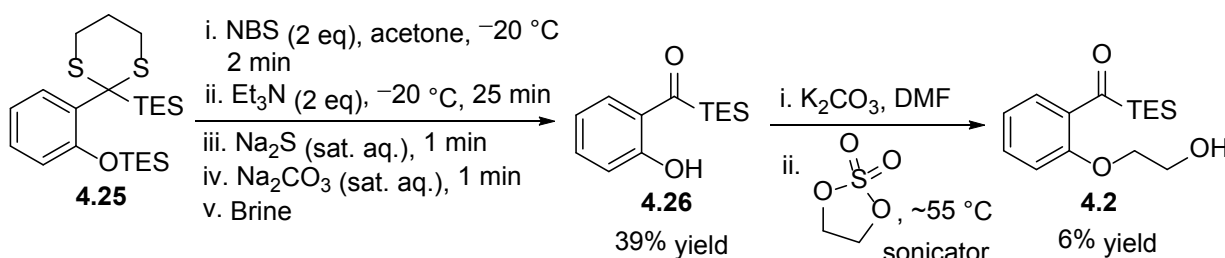


Scheme 4.14: Synthetic Route to Dithiane Intermediate **4.25**.

Oxidation to the acylsilane, however proved to be operationally difficult due to insufficient purification to separate excess NBS, and was also low yielding. Subjection of the silylated dithiane **4.25** to NBS resulted in a bright red mixture, which was challenging to purify (**Scheme 4.15**). The bright yellow acylsilane seemed to co-spot with at least one other by-product of the reaction as determined by TLC analysis. Regardless of the low yield and slight impurity, acylsilane **4.26** was subjected to

potassium bicarbonate in the presence of 1,3,2-dioxathiolane 2,2-dioxide to yield acylsilane

4.27.



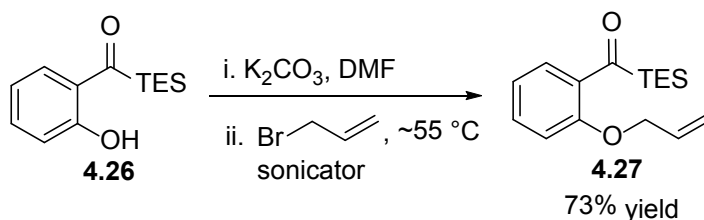
Scheme 4.15: End Game to Furnishing Acylsilane **4.2**.

Whereas time did not permit full characterization of acylsilane **4.2**, ^1H NMR and mass spec data are in agreement with the desired compound. The synthetic scheme outlined above is potentially a viable route to the desired product. With yields unoptimized, there is certainly room for improvement. The salicylaldehyde route is the shortest and most straight-forward route we have attempted to date and should be easily scaled up to gram quantities.

4.4 Initial Efforts towards the Intramolecular Cross Coupling of Acyl Silanes and Olefins

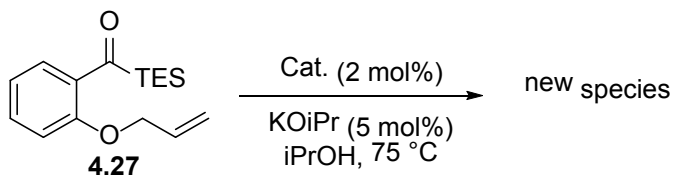
While attempting to synthesize the intramolecular acylsilanes **4.1** and **4.2**, we also wanted to test the coupling capabilities of acylsilanes and olefins, as described in the original proposal (**Section 3.3.1**). To the best of our knowledge, there have been no examples in the literature of an intramolecular coupling of acylsilane and olefins. To test the reaction, we decided to synthesize an olefin-containing analog of acylsilane **4.2**. Acylsilane **4.27** was accessed in a similar fashion to the above substrate by subsection of

acylsilane **4.26** to potassium bicarbonate in the presence of allyl bromide. The reaction proceeded cleanly to afford acylsilane **4.27** in a 73% yield (**Scheme 4.16**).



Scheme 4.16: Synthetic Route to Acylsilane **4.27**.

Preliminary coupling of acylsilane **4.27** was investigated under transfer hydrogenation conditions (**Scheme 4.17**). The four catalysts outlined in **Table 3.1** were chosen as the primary test catalysts. Due to low quantities of substrate, the catalyst and base loadings were increased to 2 mol% and 5 mol%, respectively. Although preliminary data proved promising as new species with higher molecular weights were observed, concrete conclusions cannot be drawn at this time. Complete testing and analysis has not been conducted, thus further investigation of the reaction outcome is necessary. Additionally, the conversion of starting material was slow, which indicated that the reaction conditions need considerable optimization. Ongoing work in our laboratory is focused on the development of this reaction as well at the intermolecular variant discussed in the next section.



Scheme 4.17: Preliminary Intramolecular Coupling of Acylsilanes and Olefins.

4.5 Conclusions and Future Direction

The complete synthesis of a novel acylsilane has been described. We anticipated acylsilane **4.2** could undergo an intramolecular cross coupling under transfer hydrogenation conditions, in which the substrate serves as the reducing equivalent. An analog of this substrate, in which the nature of the tether was altered, has also been of synthetic interest to us. Continued efforts need to be put forth in order to complete the synthesis of acylsilane **4.1**.

The entropic advantage in utilizing a substrate in which both coupling partners are in close proximity is more favorable than an intermolecular approach, but is not the only way to overcome some of the reactivity issues we observed with the intermolecular reaction (**Table 3.1**). Another approach to encourage the catalytic coupling of acylsilanes and aldehydes would be to change the structure of the acylsilane and impose different binding modes with the catalyst.

By installing α,β -unsaturation on the acylsilane moiety, one could envision different binding modes of the acylsilane to the metal through interaction with the double bond (**Figure 4.1**). Addition of the metal-hydride could occur in a [1,2] fashion to furnish alkoxide **a**, or a [1,4] fashion to furnish enolate **b**. The reaction model has been presented by Michael Krische's group, which involves a π -allyl binding mode of the coupling partner before insertion of the alcohol or aldehyde into the metal center (see **Scheme 4.18** below).⁷⁰ Although most of the examples of this reactivity involve silylated dienes, the Krische chemistry could potentially be adapted to coupling of an α,β -unsaturated acylsilane.

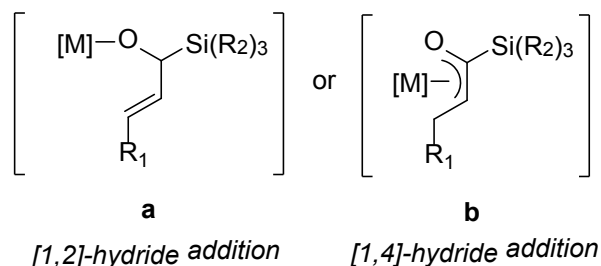
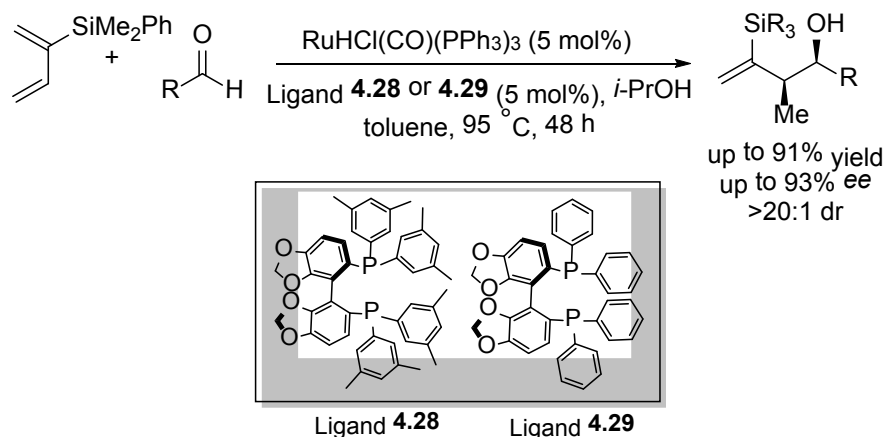


Figure 4.1: Binding of an α,β -Unsaturated Acylsilane to a Metal-Hydride.

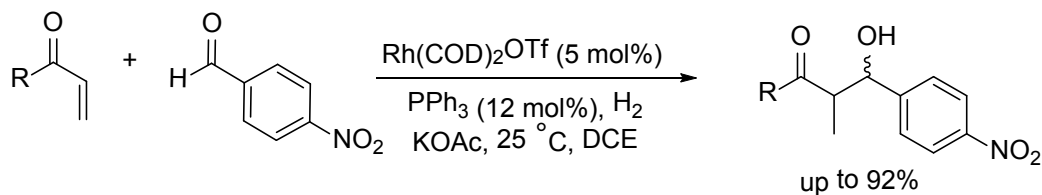
4.5.1 Coupling of Dienes and Aldehydes: A Reaction Model

Michael Krische's group at the University of Texas at Austin has been interested in various types of coupling reactions since the early 2000's and has published a large collection of excellent work on the topic.⁷¹ From enones and diynes to alkynes and dienes, numerous classes of substrates have been investigated by the Krische group and have been found to be capable of undergoing catalytic hydrogenation and transfer hydrogenation coupling reactions. Coupling of simple aldehydes or alcohols, which is most relevant to our research, to other species has been one area of interest explored by the Krische laboratory. However, the most relevant reaction model with regard to coupling reactions of acylsilanes involved silylated dienes coupled to either aldehydes or alcohols (**Scheme 4.18**).⁷² It was found that upon addition of silylated dienes to various aldehydes as well as alcohols under transfer hydrogenation conditions in the presence of a ruthenium hydride, a new C–C bond was formed to furnish diastereomer-enriched substituted alcohols in excellent yield and selectivity.



Scheme 4.18: Coupling of Silylated Dienes and Aldehydes with Ruthenium Catalysts under Transfer Hydrogenation Conditions.

Another example that could be seen as an encouraging serogate for coupling of α,β -unsaturated acylsilanes to aldehydes was published by Krische's group in 2002 that involved coupling of enones and aldehydes.⁷² In the presence of a rhodium catalyst, it was found that aromatic and aliphatic enones would undergo coupling with *p*-nitrobenzaldehyde under a hydrogen atmosphere, albeit stereochemically unselectively (**Scheme 4.19**). The two examples from the Krische group described led us to wonder if an acylsilane would behave similarly. One can imagine replacing the silylated diene with an α,β -unsaturated acylsilane to yield a very similar reaction motif. However, the outcome of changing the electronics of the system remained unknown to us.



Scheme 4.19: Coupling of Enones and Aldehydes with Rhodium Catalysts under Hydrogenation Conditions.

One of the key features of the mechanistic pathway of the coupling chemistry published by Krische's laboratory in **Scheme 4.18** is the formation of a π -allyl system. It was found that in most cases, there was a requirement for a conjugated system on the coupling partner in order to undergo the C–C bond forming step. In the case of the silylated dienes, the substrate binds to the metal center in the conformationally more accessible fashion in which the methyl group and the R group of the aldehyde are not eclipsing (**Figure 4.2**). The resulting favorable six-membered transition state is containing the two substrates and the metal center, allowing for the formation of a new σ bond. If a six-membered transition state is the key to the desired bond formation, using an α,β -unsaturated acylsilane could potentially help us overcome the activity problems we faced with the unsaturated substrate. We set out to test our hypothesis by first devising and undertaking a synthetic route to α,β -unsaturated acylsilanes.

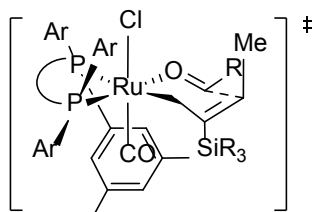
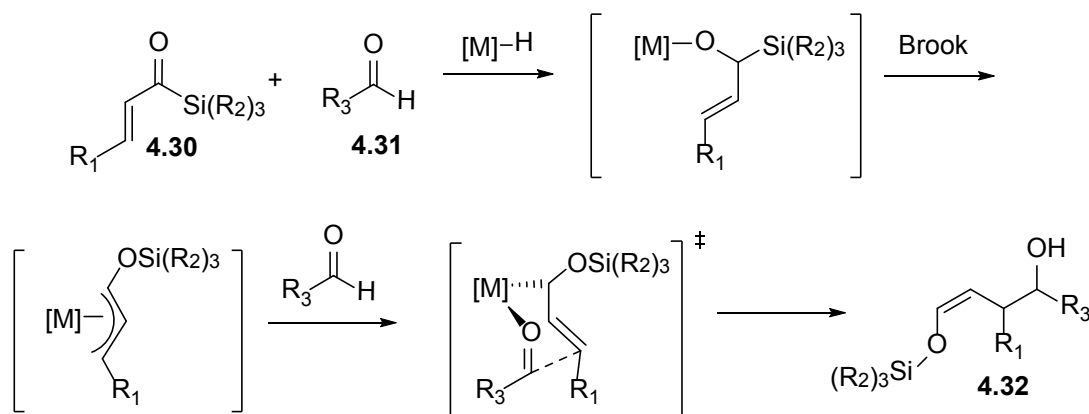


Figure 4.2: Proposed Transition State for the Coupling of Silylated Dienes and Aldehydes.

4.5.2 Experimental Design of the Coupling of α,β -Unsaturated Acylsilanes with Aldehydes and Synthesis of α,β -Unsaturated Acylsilanes

Based heavily on the published work by Michael Krische's group, we set out to accomplish an intermolecular coupling of acylsilanes and aldehydes from a different approach than that outlined in **Chapter 3**. The proposed mechanistic aspects of

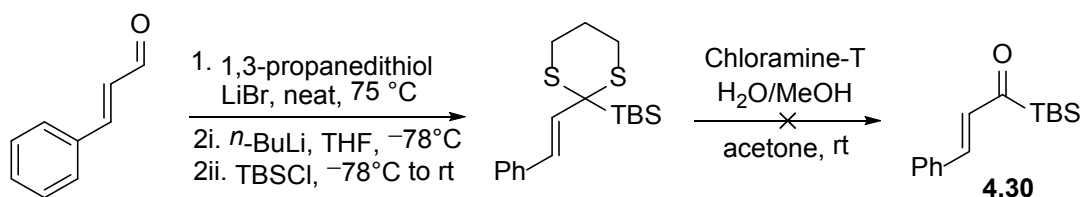
Krische's coupling reactions gave us clues as to what type of acylsilane substrate might be more accommodating for the reaction. α,β -Unsaturated acylsilanes posed as a good model due to the fact that the added unsaturation could open the door to a π -allyl bound intermediate with the metal center. We proposed that the binding of acylsilane **4.30** would result in a Brook rearrangement, followed by coordination of aldehyde **4.31**. The outcome would be the synthesis of unsaturated silyl ethers, such as **4.32** shown in **Scheme 4.20**.



Scheme 4.20: Proposed Reaction and Transition State for the Coupling of α,β -Unsaturated Acylsilanes and Aldehydes.

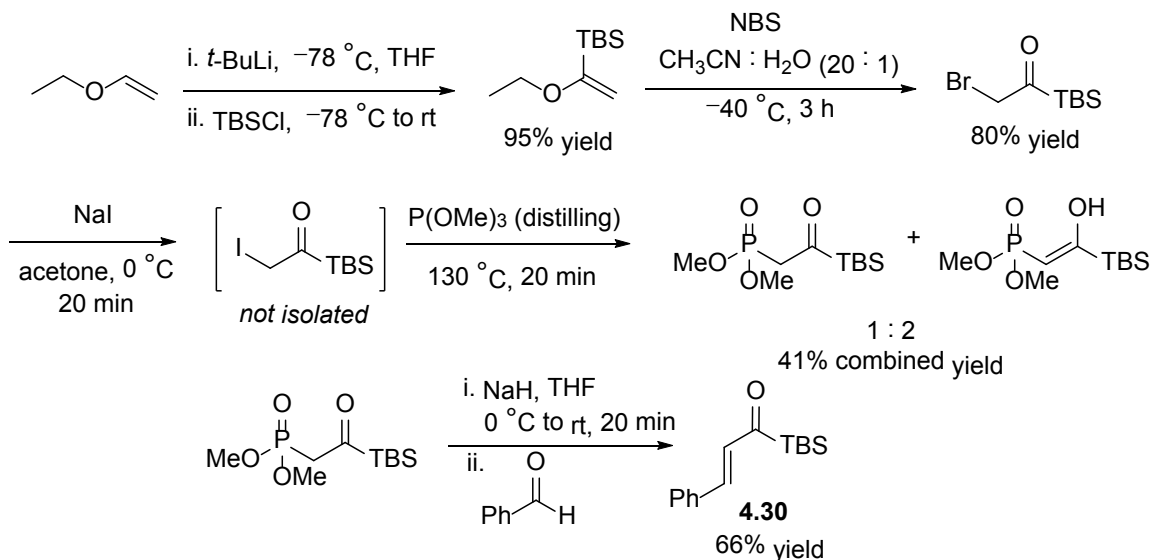
Before we could begin testing the hypothesis, α,β -unsaturated acylsilane **4.30** had to be synthesized. Most of the work performed on the synthesis and testing of acylsilane **4.30** was carried out by Lauren Yablon, an undergraduate working on the project. We had hoped that a similar dithiane route to that outlined in **Scheme 2.5** would allow for a simple synthesis of various α,β -unsaturated acylsilanes. Unfortunately, oxidation with

chloramine-T did not furnish the acylsilane, and other oxidation conditions were not tested (**Scheme 4.21**).



Scheme 4.21: Attempted Synthetic Route to Accessing α,β -Unsaturated Acylsilane **4.30**.

One route by Rich Danheiser and coworkers detailed using a Horner-Wadsworth-Emmons reaction as the ultimate step in the synthesis in a divergent synthesis of α,β -unsaturated acylsilanes.⁷³ We deemed this route the most efficient because it would allow for building a library of α,β -unsaturated acylsilanes in one step from the Horner-Wadsworth-Emmons phosphonate by simply changing the aldehyde used in the final step. The synthesis of α,β -unsaturated acylsilane **4.30** proved fairly straightforward beginning from commercially available ethyl vinyl ether through the known five-step route (**Scheme 4.22**).



Scheme 4.22: Synthetic Route to Accessing α,β -Unsaturated Acylsilane **4.30**.

Ongoing work in our lab has been geared towards the investigation of the cross coupling of α,β -unsaturated acylsilanes and aldehydes. Transfer hydrogenation conditions are currently being screened with different metal catalysts in order to access substituted silyl ethers in a novel fashion. To the best of our knowledge, the coupling of α,β -unsaturated acylsilanes with aldehydes has never been demonstrated before, which makes the proposed reaction an important tool for further development of organic reactions.

As previously mentioned, demonstrating the desired coupling reaction on an intermolecular level is important, but there are other reactivity options available. An intramolecular approach utilizing acylsilane **4.2** is also a viable option to demonstrate a metal-catalyzed Brook rearrangement and cross coupling. Continued efforts towards the accomplishment of these goals are currently underway in our laboratory.

4.6 Experimental

4.6.1 General Information

General Procedures

Unless otherwise stated, all manipulations were carried out in oven-dried glassware under a nitrogen atmosphere using standard Schlenk line techniques.³⁶ Flash column chromatography, driven by compressed air, was performed with ZEOPrep 60 Eco 40-63 μm silica gel. Analytical thin-layer chromatography (TLC) was performed using 250 μm Silica Gel 60 plates purchased from EMD Separations Technologies. TLC plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate or potassium permanganate stains.

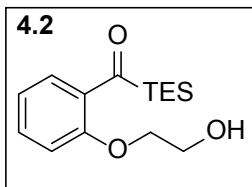
Materials

Solvents were used after passage through alumina columns under a blanket of argon and degassed *in vacuo*, except the following: isopropanol was refluxed over CaH_2 then distilled and degassed and 1,4-dioxane was distilled and degassed, methanol was used without any drying or purification. All reagents were purchased from Sigma Aldrich except the following: 1,3-propanedithiol was purchased from Alfa Aesar, chloramine-T was purchased from TCI America, TESCI was purchased from Oakwood Chemicals. NBS was recrystallized according to literature procedure prior to use.⁷⁴ Potassium bicarbonate was finely ground in a mortar and pestle and oven-dried for 24 h prior to use. IBX and 1,3,2-dioxathiolane 2,2-dioxide were synthesized according to literature procedure.^{75,76} KOi-Pr was synthesized according to patent procedure and stored in the glovebox under a nitrogen atmosphere.⁷⁷

Instrumentation

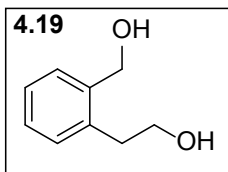
Infrared spectra were recorded on a Bruker Alpha-p spectrometer. Bands are reported as strong (s), medium (m), weak (w), broad strong (bs), broad medium (bm), and broad weak (bw). Ozonolysis was carried out on a Pacific Ozone Technology Ozonizer, Model Lab 11. ^1H Nuclear Magnetic Resonance (NMR) spectra for characterization were recorded on a Varian VNMRS (500 MHz) or VNMRS (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CHCl_3 : $\delta 7.26$). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtt = doublet of triplet of triplets, t = triplet, td = triplet of doublets, dq = doublet of quartets, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian VNMRS (125 MHz) or VNMRS (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CDCl_3 : $\delta 77.16$). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry Facility. Gas chromatograms (GC, GCMS) were obtained on a Shimadzu 2014 GCFID (Shimadzu SHRXI-5MS column, 15 m x 0.25 mm x 0.25 μm) and an Agilent 7820A GC/5975 MSD (Zebron ZB-5 column, 30 m x 0.25 mm x 0.25 μm).

4.6.2 Experimental Procedures and Characterization Data



Synthesis of (2-(2-hydroxyethoxy)phenyl)-(trimethylsilyl)methanone 4.2. To a 7 mL scintillation vial was added (2-hydroxyphenyl)-(trimethylsilyl)methanone (28.3 mg,

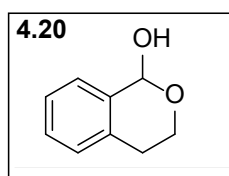
0.120 mmol, 1.00 equiv.) dissolved in DMF (1 mL). To the vial was added K_2CO_3 (33.0 mg, 0.239 mol, 2.00 equiv.) and then 1,3,2-dioxathiolane 2,2-dioxide (14.8 mg, 0.119 mol, 1.00 equiv.). The vial was sealed under argon and then sonicated at 55 °C. The mixture was allowed to react for 22 hr, during which time it turned a darker red/orange color. To the vial was then added water (10 mL) and 1M H_2SO_4 (5 mL) and the product was extracted with ethyl acetate until all yellow color was extracted from aqueous layer. The combined organic layers were washed with more water (2 x 10 mL) and brine (10 mL) and then dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield an orange oil. The crude mixture was passed through a plug of silica (20% EtOAc, hexanes v/v) to yield a yellow oil, but was not isolated analytically pure. HRMS (ESI +) Calcd. mass $C_{15}H_{24}O_3Si$ $[M+H]^+$: 281.1573; Found 281.1565.



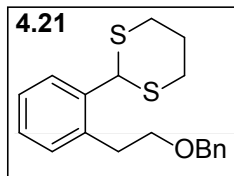
Synthesis of 2-(2-(hydroxymethyl)phenyl)ethan-1-ol 4.19. To a 100 mL round bottom flask was added indene (4.13 g, 0.036 mol, 1.00 equiv.) dissolved in a 10:1 mixture of MeOH (30 mL) and CH_2Cl_2

(3.4 mL). The solution was allowed to stir at room temperature for 5 minutes. Then the solution was cooled to -78 °C and O_3 was passed through until the solution turned a dark blue color which persisted (~ 15 minutes). Nitrogen was then passed through the solution until it was colorless. $NaBH_4$ (5.35 g, 0.141 mol, 4.00 equiv.) was then added to the

solution slowly, and the mixture allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl (100 mL) and water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated by rotary evaporation to yield a clear colorless oil. The crude reaction mixture was purified by flash silica gel chromatography (70% EtOAc, hexanes v/v) to yield a clear, colorless oil (1.35 g, 24.6%). Spectroscopic data were consistent with literature values.⁷⁸



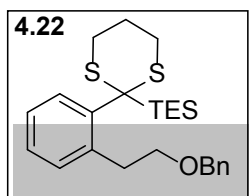
Synthesis of 1-hydroxyisochroman 4.20. To a 10 mL pear shaped flask was added IBX (193 mg, 0.689 mmol, 1.05 equiv.) dissolved in DMSO (1.5 mL) which was allowed to stir at room temperature until almost completely homogenous. To the flask was then added 2-hydroxymethyl(2'-hydroxyethyl)benzene (100 mg, 0.657 mmol, 1.00 equiv.) dissolved in DMSO (0.5 mL). The solution was allowed to stir at room temperature for 3 h. The reaction was quenched with water (4 mL) and CH_2Cl_2 (4 mL) was added. The slurry was then filtered through Celite® and the solid was washed with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was further washed with water (100 mL) to remove any DMSO and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated by rotary evaporation to yield a slightly yellow oil. The crude product was purified via column chromatography (20% EtOAc, 1% Et_3N , hexanes to 40% EtOAc, 1% Et_3N , hexanes, R_f = 0.15 in 20% EtOAc, 1% Et_3N , hexanes) to yield a slightly off-white solid (35.5 mg, 34.4%). Spectroscopic data were consistent with literature values.⁷⁹



Synthesis of 2-(2-(2-(benzyloxy)ethyl)phenyl)-1,3-dithiane 4.21. To a 10 mL pear-shaped flask was added 2-(2-(1,3-dithian-2-yl)phenyl)ethan-1-ol (45.2 mg, 0.188 mmol, 1.00 equiv.), which was dissolved in THF (1 mL) and allowed to stir at room temperature for 5 minutes. The reaction mixture was cooled to 0 °C and then NaH (8.9 mg, 0.22 mmol, 1.2 equiv., 60% w/w in mineral oil) was added, which resulted in gas evolution. The reaction mixture was allowed to stir for 10 minutes and was then warmed to ambient temperature and allowed to stir for 30 minutes. The reaction mixture was then cooled back down to 0 °C and benzyl bromide (25 μ L, 0.21 mmol, 1.1 equiv.) was then added dropwise. Immediately after benzyl bromide addition, 1 drop of 15-crown-5 was added. The mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was then quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with more water (3 x 10 mL) and then washed with brine (10 mL). The organic layer was then dried over Na₂SO₄, filtered and concentrated via rotary evaporation to yield a milky white oil (46.4 mg, 75%). The oil was purified via column chromatography (1% Et₃N, 10% EtOAc, hexanes v/v/v).

R_f = 0.36 (1% Et₃N, 10% EtOAc, hexanes v/v/v). ¹H NMR (500 MHz, CDCl₃) δ 7.64 – 7.60 (m, 1H), 7.38 – 7.17 (m, 8H), 5.40 (s, 1H), 4.55 (s, 2H), 3.74 (t, J = 7.5 Hz, 2H), 3.08 (t, J = 7.5 Hz, 2H), 3.02 (ddd, J = 14.9, 13.1, 2.4 Hz, 2H), 2.87 (dt, J = 14.5, 4.0 Hz, 2H), 2.16 (dtt, J = 13.8, 4.6, 2.4 Hz, 1H), 1.99 – 1.86 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 140.10, 138.48, 137.66, 137.06, 136.89, 135.86, 130.37, 128.66, 128.50, 128.40, 127.80, 127.71, 127.34, 73.19, 71.16, 48.10, 33.63, 32.54, 25.34. IR (neat) 2924

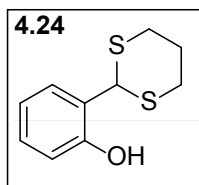
(bw), 2896 (bw), 2853 (bw), 1487 (w), 1453 (w), 1421 (w), 1361 (w), 1275 (m), 1260 (m), 1170 (bw), 1092 (s), 1050 (s), 1027 (s), 910 (w), 880 (w), 800 (m), 747 (s), 697 (s), 676 (m). HRMS (ESI +) Calcd. mass $C_{19}H_{22}OS_2 [M+H]^+$: 331.1190; Found 331.1181.



Synthesis of (2-(2-(2-(benzyloxy)ethyl)phenyl)-1,3-dithian-2-yl)triethylsilane 4.22. To an oven-dried 25 mL round-bottom flask

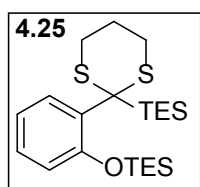
fitted with 180° joint was added 2-(2-(2-(benzyloxy)ethyl)phenyl)-1,3-dithiane (44.0 mg, 0.133 mmol, 1.00 equiv.) dissolved in THF (2.2 mL) and cooled to 0 °C. To the reaction mixture was added *n*-BuLi (90 μ L, 0.23 mmol, 1.7 equiv.) dropwise, which immediately turned the mixture bright yellow. The mixture was then allowed to warm to ambient temperature then warmed to 35 °C for 10 minutes. The reaction mixture was then cooled back down to 0 °C and TESCl (38 μ L, 0.23 mmol, 1.7 equiv.) was added to the flask. The mixture was then warmed to ambient temperature and allowed to stir for 3 h. The mixture was then quenched with saturated NH_4Cl (10 mL) and water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield a slightly yellow oil. The oil was purified via column chromatography (0.5% Et_3N , 1% $EtOAc$, hexanes v/v/v) but could not be isolated analytically pure.

R_f = 0.35 (0.5% Et_3N , 1% $EtOAc$, hexanes v/v/v).



Synthesis of 2-(1,3-dithian-2-yl)phenol 4.24. To an oven-dried 100 mL round-bottom flask fitted with a 180° joint was added salicylaldehyde (2.44 g, 20.0 mmol, 1.00 equiv.), 4 Å molecular sieves (1.00 g) and

CH₂Cl₂ (40 mL). To the flask was then added 1,3-propanedithiol (2.06 mL, 20.5 mmol, 1.03 equiv.) and the mixture was cooled to 0 °C. To the flask was slowly added boron trifluoride diethyl etherate (5.0 mL, 41 mmol, 2.0 equiv.), which immediately lead to formation of a bright yellow solution. The reaction mixture was allowed to stir at 0 °C for 2 hr and then was slowly warmed to ambient temperature and allowed to stir for 46 hr. The reaction mixture turned more orange as time progressed. The reaction mixture was quenched with saturated NaHCO₃ (30 mL), which resulted in gas evolution. The resulting slurry was then filtered through a plug of cotton into a separatory funnel and then water (100 mL) was added. The crude mixture was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were further washed with water (4 x 100 mL) and dried over MgSO₄, filtered and concentrated by rotary evaporation to yield a white solid in slightly yellow oil. The crude mixture was subjected to purification via column chromatography (20% EtOAc, hexanes v/v) to yield a white solid (1.20 g, 28%), which was dried over P₂O₅ overnight. Spectroscopic data were consistent with literature values.^{67b}

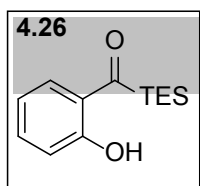


Synthesis of trimethyl(2-(2-(trimethylsilyl)-1,3-dithian-2-yl)phenoxy)-

silane 4.25. To an oven-dried 100 mL round-bottom flask fitted with 180° joint was added 2-(1,3-dithian-2-yl)phenol (1.25 g, 5.88 mol, 1.00

equiv.) which was dissolved in THF (70 mL) and then cooled to −40 °C (1:1 mixture of ethylene glycol/methanol, dry ice bath). To the flask was slowly added *n*-BuLi (6.9 mL, 21 mol, 3.5 equiv.) via syringe which immediately lead to a yellow solution that was allowed to warm to 0 °C and stir for 1 h. The solution was then cooled back down to −40 °C and TESCl (3.49 mL, 20.3 mol, 3.50 equiv.) was added via syringe. The solution was

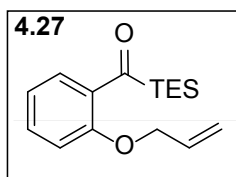
allowed to slowly warm to ambient temperature and stir for 2.5 h. The reaction mixture was then quenched with saturated NH_4Cl (100 mL) and water (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried over MgSO_4 , filtered and concentrated by rotary evaporation. The crude mixture was purified by filtration through a plug of silica gel (first flush with hexanes discarded, then 20% CH_2Cl_2 , hexanes v/v) and the solvent was removed via rotary evaporation to yield a clear, colorless oil (2.51 g, 97%). Spectroscopic data were consistent with literature values.^{67b}



Synthesis of (2-hydroxyphenyl)(trimethylsilyl)methanone 4.26. To a

100 mL round-bottom flask was added trimethyl(2-(2-(trimethylsilyl)-1,3-dithian-2-yl)phenoxy)silane (1.16 g, 2.63 mol, 1.00 equiv.) dissolved in acetone (10 mL) and cooled to $-20\text{ }^{\circ}\text{C}$ (2:1 mixture of ethylene glycol/methanol, dry ice bath). NBS (936 mg, 5.26 mol, 2.00 equiv.) dissolved in acetone (10 mL) was added dropwise to the solution, which immediately produced a dark yellow then red solution. Et_3N (734 μL , 5.26 mol, 2.00 equiv.) was added immediately following NBS addition, which turned the solution a deeper red. The solution was allowed to stir at $-20\text{ }^{\circ}\text{C}$ for 25 minutes and then a saturated aqueous solution of Na_2S (2 mL) was added. After 1 minute, a saturated solution of Na_2CO_3 (2 mL) was added and then after another minute had passed brine was added (2 mL). To the mixture was then added a 1:1 mixture of CH_2Cl_2 and hexanes ($\sim 50\text{ mL}$) and the entire mixture was passed through a filter frit of Celite® and silica gel until all the yellow color was abstracted. The organic layer was dried over MgSO_4 , filtered and concentrated by rotary evaporation to yield a dark red oil with solid precipitate in it. The crude mixture was purified via

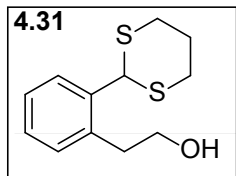
column chromatography (1% EtOAc, hexanes v/v to 2% EtOAc, hexanes v/v) to yield a bright yellow oil (243 mg, 38.6%). Spectroscopic data were consistent with literature values.^{67b}



Synthesis of (2-(allyloxy)phenyl)(trimethylsilyl)methanone 4.27. To

a 25 mL scintillation vial was added (2-hydroxyphenyl)(trimethylsilyl)methanone (129 mg, 0.546 mmol, 1.00 equiv.) dissolved in DMF (2.2 mL). To the vial was then added K_2CO_3 (226 mg, 1.64 mmol, 3.00 equiv.) and then allyl bromide (52 μ L, 0.60 mmol, 1.1 equiv.). The vial was sealed under argon and then sonicated at 55 °C. The mixture was allowed to react for 22 hr and then quenched with water (20 mL) and extracted with ethyl acetate until all yellow color was extracted from aqueous layer. The combined organic layers were washed with more water (2 x 10 mL) and then brine (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated by rotary evaporation to yield an orange oil. The crude mixture was purified by passage through Celite and silica gel (hexanes flush discarded then 20% EtOAc, hexanes v/v collected). The solvent was removed via rotary evaporation to yield a bright yellow oil (111 mg, 73%).

R_f = 0.22 (1% EtOAc, hexanes v/v). 1H NMR (500 MHz, $CDCl_3$) δ 7.37 (ddd, J = 8.4, 7.3, 1.8 Hz, 1H), 7.26 – 7.24 (m, 1H), 6.97 (td, J = 7.4, 0.9 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.07 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.39 (dq, J = 17.3, 1.5 Hz, 1H), 5.32 (dq, J = 10.4, 1.3 Hz, 1H), 4.65 (dt, J = 5.6, 1.4 Hz, 2H), 0.95 – 0.90 (m, 9H), 0.83 – 0.76 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 239.97, 157.39, 135.43, 132.82, 132.64, 126.66, 121.19, 118.91, 111.92, 69.29, 7.62, 2.95. IR (neat) 2953 (m), 2911 (m), 2875 (m), 1605 (m), 1586 (m), 1478 (m), 1447 (m), 1422 (w), 1283 (m), 1261 (w), 1235 (m), 1221 (m),



1192 (w), 1161 (w), 1107 (w), 1047 (w), 1010 (m), 921 (m), 754 (s), 733 (s), 664 (w). HRMS (ESI +) Calcd. mass $C_{16}H_{24}O_2Si$ $[M+H]^+$: 277.1624; Found 277.1623. *Synthesis of 2-(2-(1,3-dithian-2-*

yl)phenyl)ethan-1-ol 4.31. To a 25 mL pear shaped flask was added 1-hydroxyisochroman (194 mg, 1.30 mmol, 1.00 equiv.) dissolved in $CHCl_3$ (6 mL, passed through K_2CO_3). 1,3-propanedithiol (129 μ L, 1.28 mmol, 1.00 equiv.) was added to the flask and stirred at ambient temperature for 5 minutes. Tetrafluoroboric acid diethyl ether (175 μ L, 1.27 mmol, 1.27 equiv.) was then added to the flask dropwise which immediately turned the solution cloudy then clearer and slightly yellow within minutes. The reaction was allowed to progress for 25 h at room temperature and then the mixture was quenched with water (40 mL) and 1M NaOH (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The organic layers were combined and washed with additional water (5 mL), 1M NaOH (5 mL) and then brine (5 mL). The combined organic layers were washed with more 1M NaOH (10 mL) and then washed with brine (30 mL). The organic layer was then dried with Na_2SO_4 , filtered and concentrated by rotary evaporation to yield a milky-white oil (268 mg, 87.8%). The oil was purified via column chromatography (1% Et_3N , 50% EtOAc, hexanes v/v/v).

R_f = 0.24 (1% Et_3N , 50% EtOAc, hexanes v/v/v). 1H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.64 (m, 1H), 7.29 – 7.22 (m, 2H), 7.21 – 7.17 (m, 1H), 5.43 (s, 1H), 3.90 (t, J = 6.4 Hz, 2H), 3.10 (ddd, J = 14.9, 12.7, 2.4 Hz, 2H), 3.02 (t, J = 6.5 Hz, 2H), 2.91 (ddd, J = 14.6, 4.2, 3.2 Hz, 2H), 2.19 (dtt, J = 13.6, 4.4, 2.4 Hz, 1H), 1.94 (dtt, J = 14.2, 12.7, 3.0 Hz, 1H), 1.74 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.81, 130.62, 128.94, 128.66, 127.56, 105.15, 63.95, 48.15, 36.47, 32.61, 25.28, 14.35. IR (neat) 3376 (bw), 2938

(bm), 2896 (m), 1486 (m), 1448 (w), 1421 (m), 1275 (m), 1170 (w), 1091 (w), 1041 (s),
909 (w), 881 (w), 801 (w), 749 (s), 726 (m), 675 (m), 589 (w), 481 (w).

4.6.3 NMR Spectral Data

Figure 4.3: ^1H NMR of 2-(2-(2-(benzyloxy)ethyl)phenyl)-1,3-dithiane (4.21)

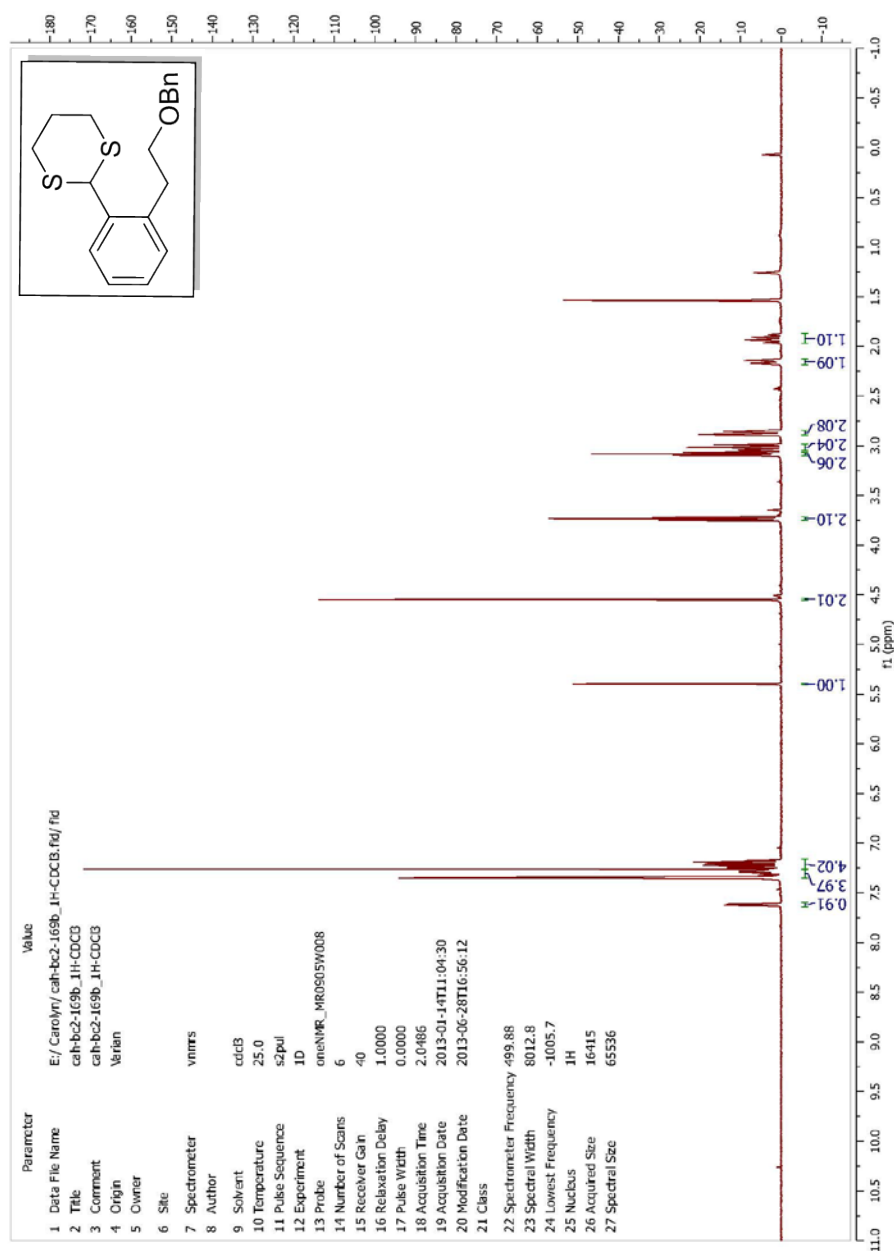


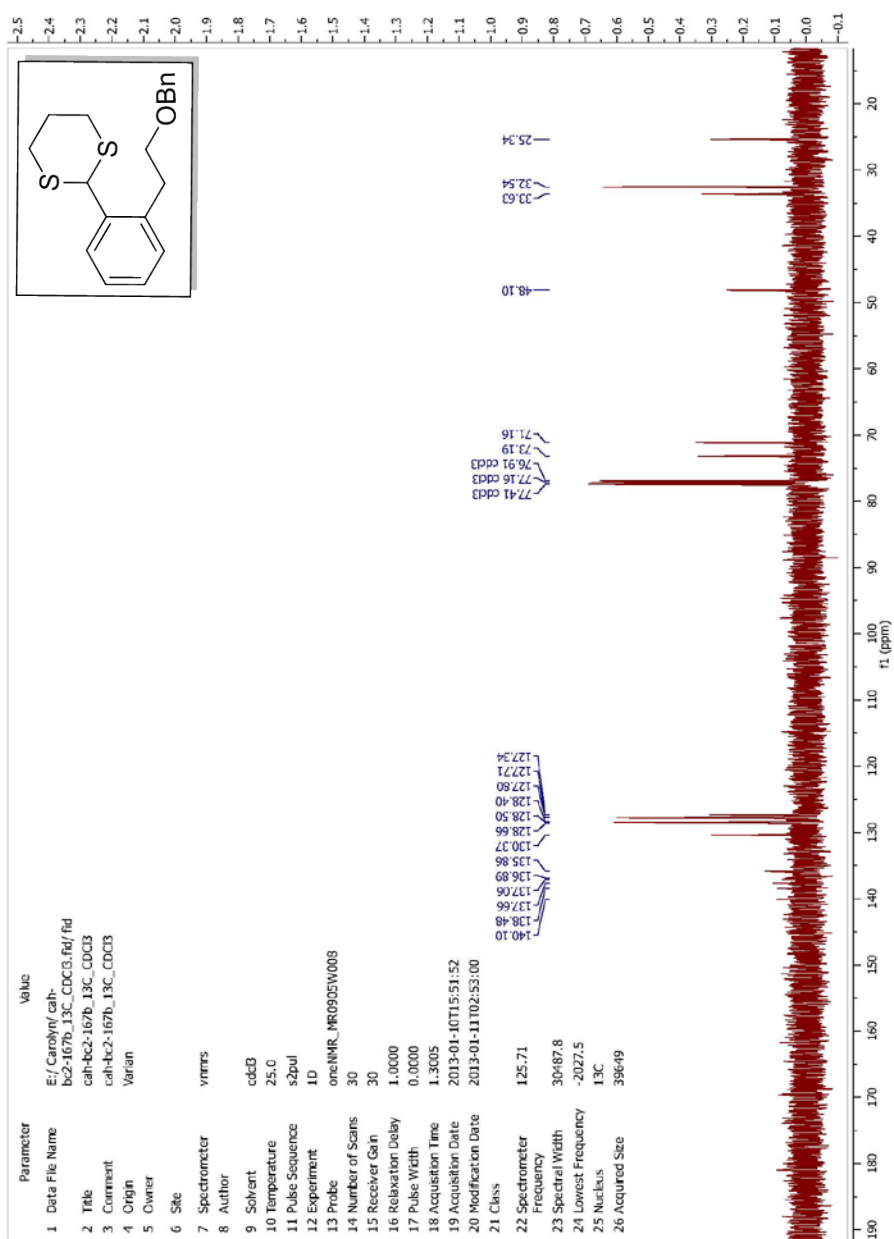
Figure 4.4: ^{13}C NMR of 2-(2-(2-(benzyloxy)ethyl)phenyl)-1,3-dithiane (4.21)

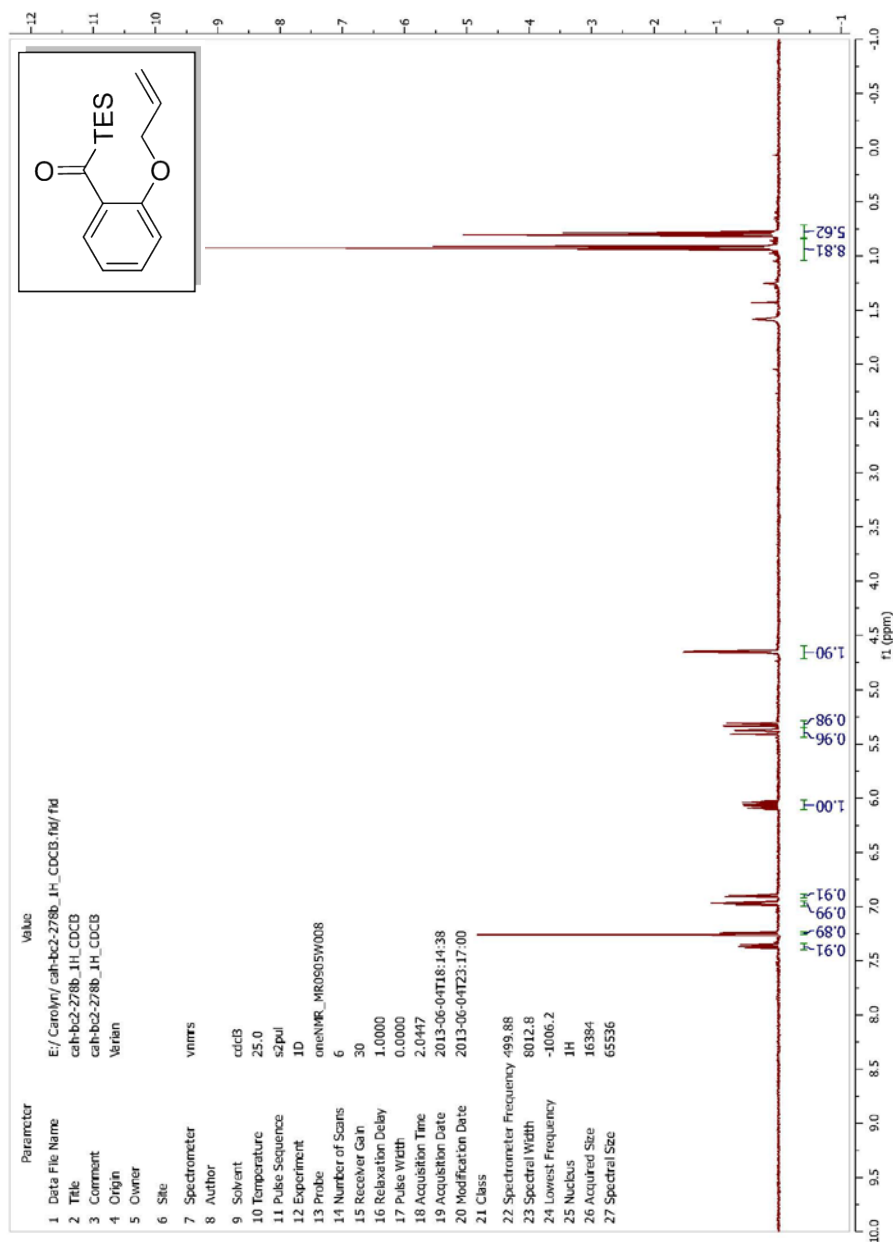
Figure 4.5: ^1H NMR of (2-(allyloxy)phenyl)(trimethylsilyl)methanone (4.27)

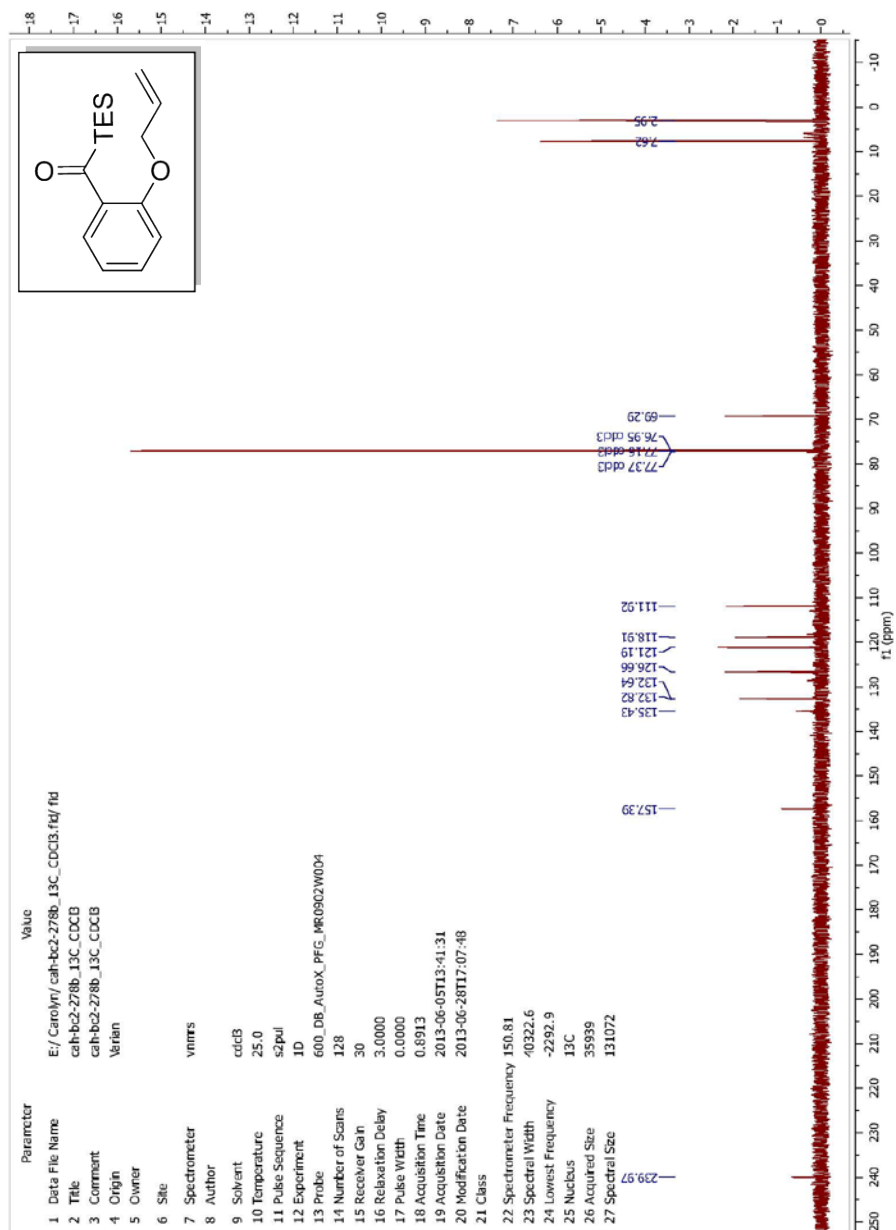
Figure 4.6: ^{13}C NMR of (2-(allyloxy)phenyl)(trimethylsilyl)methanone (4.27)

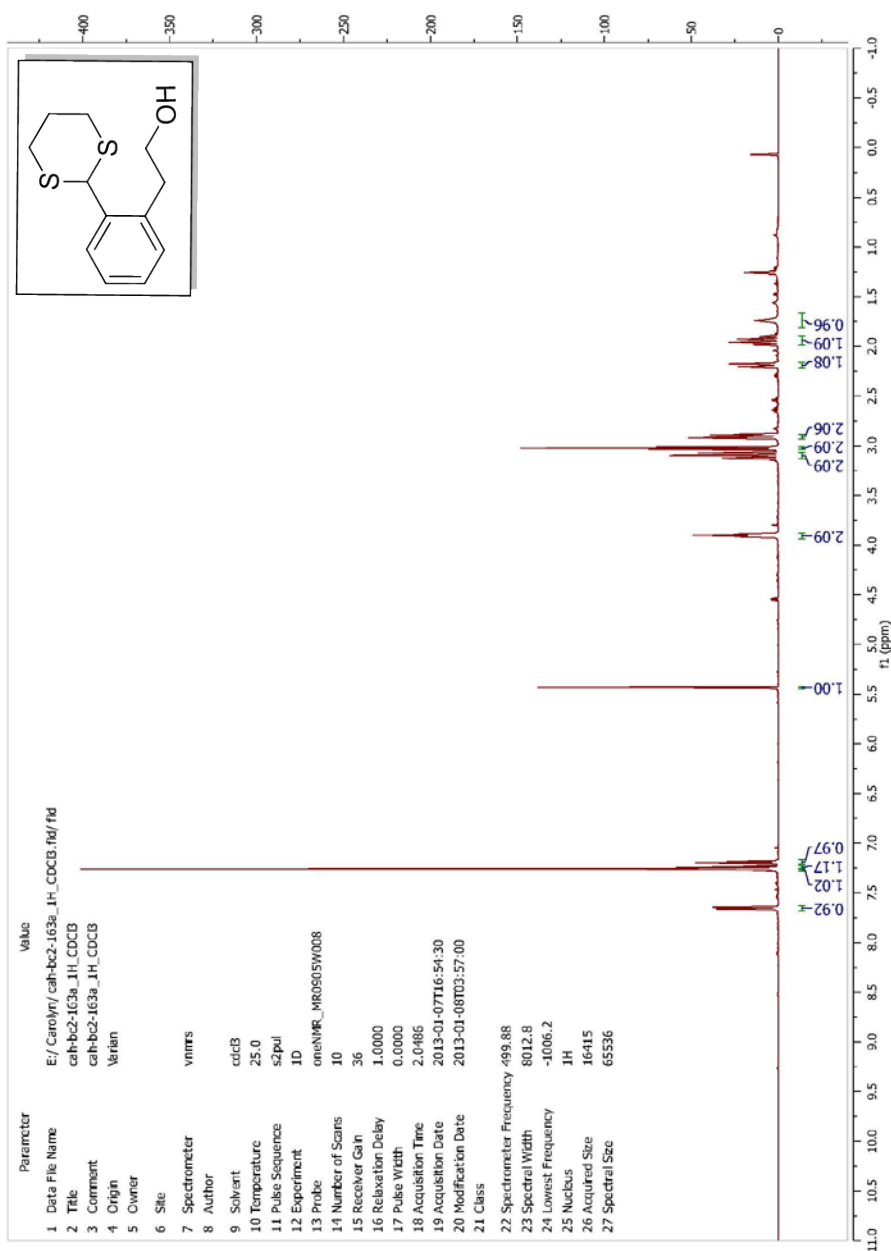
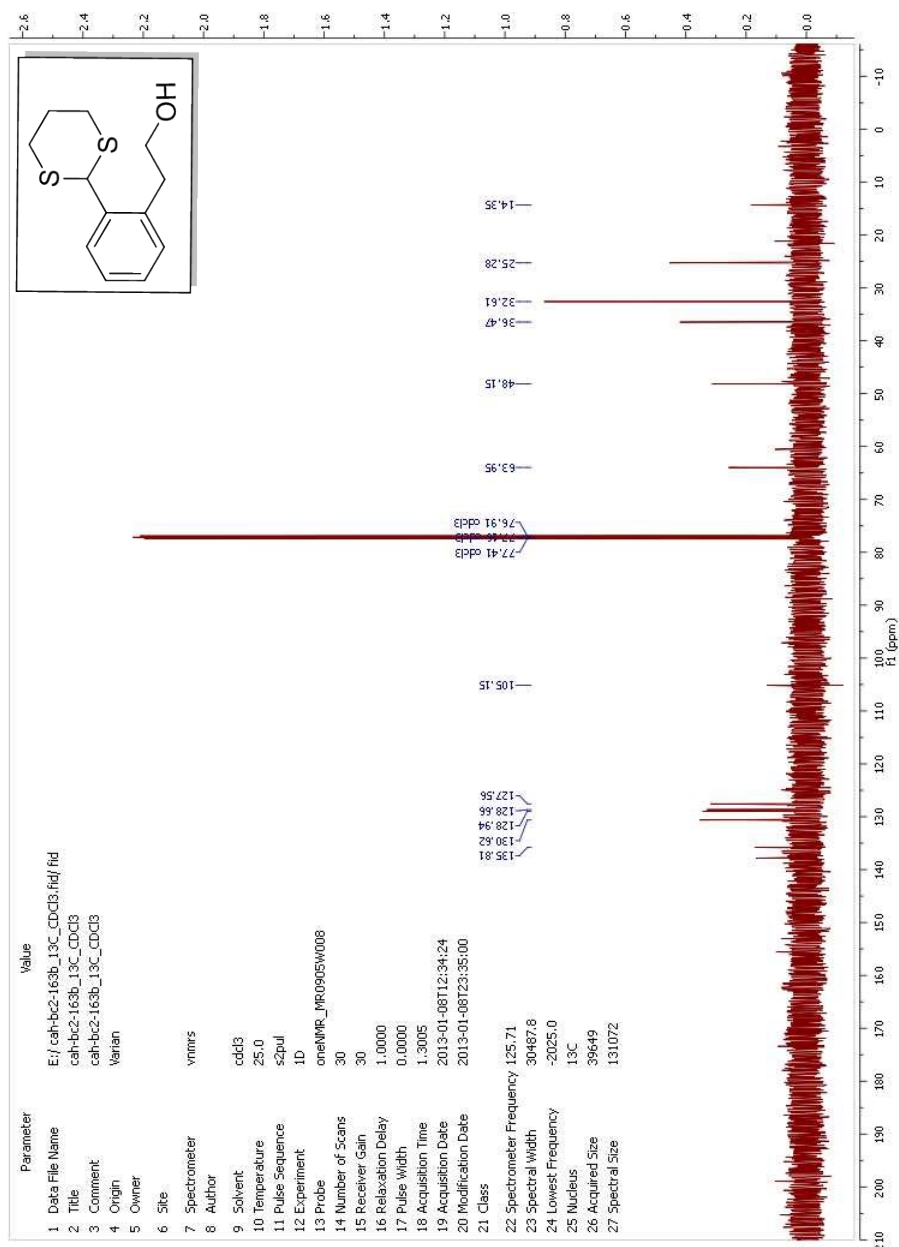
Figure 4.7: ¹H NMR of 6-Hydroxyethyl-1,3-dithiane benzene (4.31)

Figure 4.8: ^{13}C NMR of 6-Hydroxyethyl-1,3-dithiane benzene (4.31)



4.7. References

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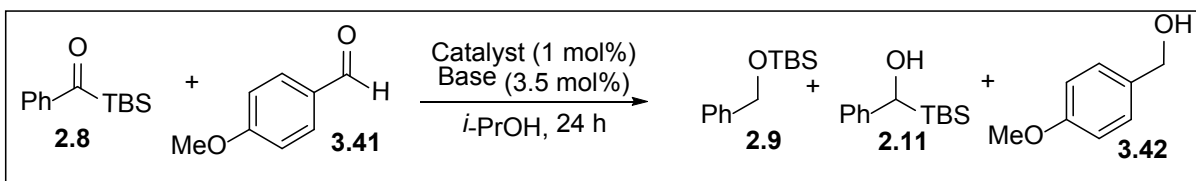
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Appendix 1

Cross Coupling Screen of Acylsilane 2.8 and Aldehyde 3.41 with Various

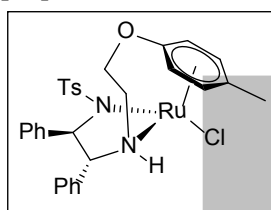
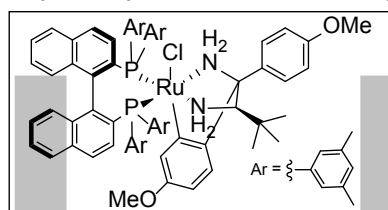
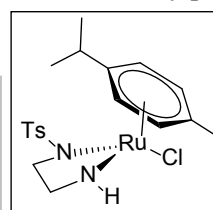
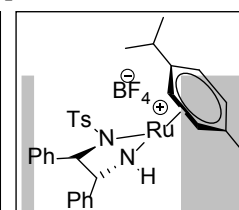
Ruthenium and Rhodium Catalysts under Transfer Hydrogenation



Entry	Temp	Catalyst	Base	Conv. 2.8	Yield 2.9	Yield 2.11	Conv. 3.41	Yield 3.42
1	75°C	2.12	NaOH	96%	38%	2%	66%	66%
			KOH	92%	46%	2%	94%	83%
			NaOiPr	84%	7%	70%	100%	88%
			KOiPr	98%	52%	4%	96%	87%
			KOiPr ^a	40%	25%	10%	94%	90%
			KOiPr ^b	77%	17%	60%	99%	60%
2		RuCl ₂ (PPh ₃) ₃	NaOH	60%	2%	50%	94%	79%
			KOH	20%	2%	8%	97%	90%
			NaOiPr	52%	---	50%	98%	87%
			KOiPr	71%	4%	60%	97%	88%
3		RuCl ₂ (dppe) ₂ <i>trans</i>	NaOH	24%	5%	---	32%	9%
			KOH	33%	3%	---	42%	12%
			NaOiPr	20%	5%	---	17%	11%
			KOiPr	20%	2%	---	30%	8%
4		RuCl ₂ (Pt-Bu ₃) ₃	NaOH	29%	3%	26%	93%	90%
			KOH	34%	3%	29%	92%	86%
			NaOiPr	10%	---	---	---	---
			KOiPr	44%	7%	37%	97%	90%
5	62°C ^c	RuCl ₂ (PCy ₃) ₃	NaOH	0%	---	---	35%	35%
			KOH	0%	---	---	7%	7%
			NaOiPr	0%	---	---	23%	8%
			KOiPr	0%	---	---	29%	12%
6		RuCl ₂ (dcpe) ₂ <i>trans</i>	NaOH	0%	---	---	43%	18%
			KOH	0%	---	---	40%	18%
			NaOiPr	22%	---	20%	53%	48%
			KOiPr	13%	2%	7%	30%	22%
7		RuH ₂ (PPh ₃) ₄	---	8%	2%	4%	31%	29%

8		RuClH(PPh ₃) ₄	NaOH	28%	2%	8%	64%	37%
			KOH	18%	2%	7%	53%	35%
			NaOiPr	20%	2%	7%	57%	41%
			KOiPr	22%	2%	6%	48%	27%
9	54°C ^d	RuHCl(PPh ₃)CO	NaOH	<5%	---	<5%	25%	25%
			KOH	<5%	---	<5%	30%	30%
			NaOiPr	<5%	---	<5%	10%	10%
			KOiPr	<5%	---	<5%	35%	35%
10		3.43	NaOH	10%	---	8%	95%	90%
			KOH	45%	5%	40%	95%	90%
			NaOiPr	5%	---	<5%	40%	38%
			KOiPr	50%	15%	35%	95%	90%
11	54°C ^d	RhCl(PPh ₃) ₃	NaOH	95%	---	87%	>95%	91%
			KOH	95%	---	90%	>95%	88%
			NaOiPr	5%	---	2%	<5%	<5%
			KOiPr	93%	---	90%	>95%	88%
12		4.32	NaOH	32%	---	29%	>95%	89%
			KOH	27%	---	24%	>95%	90%
			NaOiPr	11%	---	11%	21%	11%
			KOiPr	18%	---	18%	>95%	90%
13		4.33	NaOH	41%	---	37%	95%	87%
			KOH	27%	---	25%	95%	85%
			NaOiPr	14%	---	13%	27%	15%
			KOiPr	28%	---	25%	95%	84%

^a1:2 ratio of **2.8** to **3.41**. ^b1:3 ratio of **2.8** to **3.41** ^c0.5 mL of THF added to catalyst for solubility purposes. ^d0.5 mL of methyl *t*-butyl ether added to catalyst for solubility purposes.

Catalyst **2.12**Catalyst **3.43**Catalyst **4.32**Catalyst **4.33**